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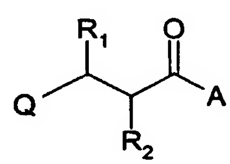
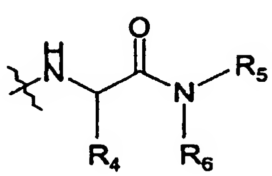


(II)



(IIA)

(IIB)

(57) Abstract: Compounds of formula (II) are antibacterial agents wherein Q represents a radical of the formula: -N(OH)CH(=O) or the formula: -C(=O)NH(OH); R_1 represents hydrogen, C_1-C_6 alkyl or C_1-C_6 alkyl substituted by one or more halogen atoms, or, except when Q is a radical of the formula: -N(OH)CH(=O), a hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkenyloxy, amino, C_1-C_6 alkylamino, or di-(C_1-C_6 alkyl)amino group; R_2 represents a substituted or unsubstituted C_1-C_6 alkyl, cycloalkyl(C_1-C_6 alkyl)- or aryl(C_1-C_6 alkyl)- group; and A represents a group of formula (IIA), or (IIB) wherein R_4 represents the side chain of a natural or non-natural alpha amino acid, and R_5 and R_6 when taken together with the nitrogen atom to which they are attached form a saturated heterocyclic first ring of 5 to 7 atoms as specified in the description.

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Antibacterial Agents

This invention relates to novel hydroxamic acid and N-formyl hydroxylamine derivatives having antibacterial activity, to methods of treatment using such compounds, and to pharmaceutical and veterinary compositions comprising such compounds.

Background to the Invention

Many classes of antibacterial agents are known, including the penicillins and cephalosporins, tetracyclines, sulfonamides, monobactams, fluoroquinolones and quinolones, aminoglycosides, glycopeptides, macrolides, polymyxins, lincosamides, trimethoprim and chloramphenicol. The fundamental mechanisms of action of these antibacterial classes vary.

Bacterial resistance to many known antibacterials is a growing problem. Accordingly there is a continuing need in the art for alternative antibacterial agents, especially those which have mechanisms of action fundamentally different from the known classes.

Amongst the Gram-positive pathogens, such as Staphylococci, Streptococci, Mycobacteria and Enterococci, resistant strains have evolved/arisen which makes them particularly difficult to eradicate. Examples of such strains are methicillin resistant *Staphylococcus aureus* (MRSA), methicillin resistant coagulase negative Staphylococci (MRCNS), penicillin resistant *Streptococcus pneumoniae* and multiply resistant *Enterococcus faecium*.

Pathogenic bacteria are often resistant to the aminoglycoside, β-lactam (penicillins and cephalosporins), and chloramphenicol types of antibiotic. This resistance involves the enzymatic inactivation of the antibiotic by hydrolysis or by formation of inactive derivatives. The β-lactam (penicillin and cephalosporin) family of antibiotics are characterised by the presence of a β-lactam ring structure. Resistance to this

family of antibiotics in clinical isolates is most commonly due to the production of a "penicillinase" (β-lactamase) enzyme by the resistant bacterium which hydrolyses the β-lactam ring thus eliminating its antibacterial activity.

Recently there has been an emergence of vancomycin-resistant strains of enterococci (Woodford N. 1998 Glycopeptide-resistant enterococci: a decade of experience. Journal of Medical Microbiology. 47(10):849-62). Vancomycin-resistant enterococci are particularly hazardous in that they are frequent causes of hospital based infections and are inherently resistant to most antibiotics. Vancomycin works by binding to the terminal D-Ala-D-Ala residues of the cell wall peptidioglycan precursor. The high-level resistance to vancomycin is known as VanA and is conferred by a genes located on a transposable element which alter the terminal residues to D-Ala-D-lac thus reducing the affinity for vancomycin.

In view of the rapid emergence of multidrug-resistant bacteria, the development of antibacterial agents with novel modes of action that are effective against the growing number of resistant bacteria, particularly the vancomycin resistant enterococci and β-lactam antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus,* is of utmost importance.

Brief Description of the Invention

This invention is based on the finding that certain hydroxamic acid and N-formyl hydroxylamine derivatives have antibacterial activity, and makes available a new group of antibacterial agents. It has been found that the compounds with which this invention is concerned are antibacterial with respect to a range of bacteria, with potency against Gram-positive organisms generally being greater than against Gram-negatives. Many of the compounds of the invention show activity against bacteria responsible for respratory infections, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.

Although it may be of interest to establish the mechanism of action of the

compounds with which the invention is concerned, it is their ability to inhibit bacterial growth that makes them useful. However, it is presently believed that their antibacterial activity is due, at least in part, to intracellular inhibition of bacterial polypeptide deformylase (PDF; EC 3.5.1.31).

All ribosome-mediated synthesis of proteins starts with a methionine residue. In prokaryotes the methionyl moiety carried by the initiator tRNA is N-formylated prior to its incorporation into a polypeptide. Consequently, N-formylmethionine is always present at the N-terminus of a nascent bacterial polypeptide. However, most mature proteins do not retain the N-formyl group or the terminal methionine residue. Deformylation is required prior to methionine removal, since methionine aminopeptidase does not recognise peptides with an N-terminal formylmethionine residue (Solbiati et al., J. Mol. Biol. 290:607-614, 1999). Deformylation is, therefore, a crucial step in bacterial protein biosynthesis and the enzyme responsible, PDF, is essential for normal bacterial growth. Although the gene encoding PDF (*def*) is present in all pathogenic bacteria for which sequences are known (Meinnel et al., J. Mol. Biol, 266:939-49, 1997), it has no eukaryotic counterpart, making it an attractive target for antibacterial chemotherapy.

The isolation and characterisation of PDF has been facilitated by an understanding of the importance of the metal ion in the active site (Groche et al., Biophys. Biochem. Res. Commun., 246:324-6, 1998). The Fe^{2+} form is highly active *in vivo* but is unstable when isolated due to oxidative degradation (Rajagopalan et al., J. Biol. Chem. 273:22305-10, 1998). The Ni^{2+} form of the enzyme has specific activity comparable with the ferrous enzyme but is oxygen-insensitive (Ragusa et al., J. Mol. Biol. 1998, 280:515-23, 1998). The Zn^{2+} enzyme is also stable but is almost devoid of catalytic activity (Rajagopalan et al., J. Am. Chem. Soc. 119:12418-12419, 1997).

Several X-ray crystal structures and NMR structures of *E. coli* PDF, with or without bound inhibitors, have been published (Chan et al., Biochemistry 36:13904-9, 1997; Becker et al., Nature Struct. Biol. 5:1053-8, 1998; Becker et al., J. Biol. Chem.

273:11413-6, 1998; Hao et al., Biochemistry, 38:4712-9, 1999; Dardel et al., J. Mol. Biol. 280:501-13, 1998; O'Connell et al., J. Biomol. NMR, 13:311-24, 1999), indicating similarities in active site geometry to metalloproteinases such as thermolysin and the metzincins.

Recently the substrate specificity of PDF has been extensively studied (Ragusa et al., J. Mol. Biol. 289:1445-57, 1999; Hu et al., Biochemistry 38:643-50, 1999; Meinnel et al., Biochemistry, 38:4287-95, 1999). These authors conclude that an unbranched hydrophobic chain is preferred at P1', while a wide variety of P2' substituents are acceptable and an aromatic substituent may be advantageous at the P3' position. There have also been reports that small peptidic compounds containing an H-phosphonate (Hu et al., Bioorg. Med. Chem. Lett., 8:2479-82, 1998) or thiol (Meinnel et al., Biochemistry, 38:4287-95, 1999) metal binding group are micromolar inhibitors of PDF. Peptide aldehydes such as calpeptin (N-Cbz-Leu-norleucinal) have also been shown to inhibit PDF (Durand et al., Arch. Biochem. Biophys., 367:297-302, 1999). However, the identity of the metal binding group and its spacing from the rest of the molecule ("recognition fragment") has not been studied extensively. Furthermore, non-peptidic PDF inhibitors, which may be desirable from the point of view of bacterial cell wall permeability or oral bioavailability in the host species, have not been identified.

<u>Related Prior Art</u>

Certain N-formyl hydroxylamine derivatives have previously been claimed in the patent publications listed below, although very few examples of such compounds have been specifically made and described:

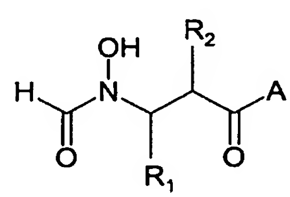
EP-B-0236872	(Roche)
WO 92/09563	(Glycomed)
WO 92/04735	(Syntex)
WO 95/19965	(Glycomed)
WO 95/22966	(Sanofi Winthrop)

WO 95/33709	(Roche)
WO 96/23791	(Syntex)
WO 96/16027	(Syntex/Agouron)
WO 97/03783	(British Biotech)
WO 97/18207	(DuPont Merck)
WO 98/38179	(GlaxoWellcome)
WO 98/47863	(Labs Jaques Logeais)

The pharmaceutical utility ascribed to the N-formyl hydroxylamine derivatives in those publications is the ability to inhibit matrix metalloproteinases (MMPs) and in some cases release of tumour necrosis factor (TNF), and hence the treatment of diseases or conditions mediated by those enzymes, such as cancer and rheumatoid arthritis.

In addition to these, US-A-4,738,803 (Roques et al.) also discloses N-formyl hydroxylamine derivatives, however, these compounds are disclosed as enkephalinase inhibitors and are proposed for use as antidepressants and hypotensive agents. Also, WO 97/38705 (Bristol-Myers Squibb) discloses certain N-formyl hydroxylamine derivatives as enkephalinase and angiotensin converting enzyme inhibitors.

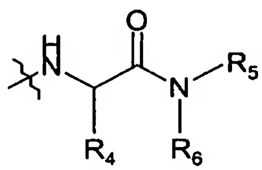
Our copending International Patent Application No. WO 99/39704 describes and claims, *inter alia*, the use of a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof in the preparation of an antibacterial composition:



(I)

wherein R_1 represents hydrogen, C_1-C_6 alkyl or C_1-C_6 alkyl substituted by one or more halogen atoms; R_2 represents a substituted or unsubstituted C_1-C_6 alkyl,

cycloalkyl(C_1-C_6 alkyl)- or aryl(C_1-C_6 alkyl)- group; and A represents a group of formula (IA), or (IB):



(IA)

(IB)

wherein R_4 represents the side chain of a natural or non-natural alpha amino acid, and R_5 and R_6 when taken together with the nitrogen atom to which they are attached form an optionally substituted saturated heterocyclic ring of 3 to 8 atoms which ring is optionally fused to a carbocyclic or second heterocyclic ring.

Very many hydroxamic acid derivatives are known. Many have been disclosed as having matrix metalloproteinase (MMP) inhibitory activity, and thus to be potentially useful for the treatment of diseases mediated by MMPs, for example cancer, arthritides, and conditions involving tissue remodeling such as wound healing, and restenosis. In addition our International Patent Application No. WO 99/59568 describes the use of analogues of the N-formylhydroxylamine derivatives of WO 99/39704 (wherein the N-formylhydroxylamine group is replaced by a hydroxamic acid group) in the preparation of an antibacterial composition.

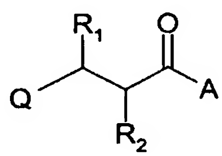
Brief Description of the Invention

This invention relates to a group of antibacterially active hydroxamic acid and and N-formyl hydroxylamine compounds which differ in structure from those of International Patent Applications Nos. WO 99/59568 and WO 99/39704, principally in the nature of the -NR_5R_6 group (see formulae (I), (IA) and (IB) above and the hydroxamic acid analogues thereof). In those applications, the term "optionally substituted" as used in relation to the saturated heterocyclic ring formed by R_5, R_6 and the nitrogen to which they are attached is defined as meaning certain specific substituents. In the present

compounds, the group $-NR_5R_6$ is also an optionally substituted saturated heterocyclic ring of 3 to 8 atoms which ring is optionally fused to a carbocyclic or second heterocyclic ring, but the substituents are different from those permitted by WO 99/59568 and WO 99/39704. The group $-NR_5R_6$ of the N-formyl hydroxylamines and hydroxamic acids of the invention is also believed to distinguish the present compounds from those known in the MMP, TNF, ACE, and enkephalinase inhibitor art.

Detailed description of the invention

The present invention provides a compound of formula (II), or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof



(II)

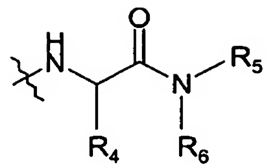
wherein

Q represents a radical of formula -N(OH)CH(=O) or formula -C(=O)NH(OH);

R_1 represents hydrogen, C_1-C_6 alkyl or C_1-C_6 alkyl substituted by one or more halogen atoms, or, except when Q is a radical of formula -N(OH)CH(=O), a hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkenyloxy, amino, C_1-C_6 alkylamino, or di-(C_1-C_6 alkyl)amino group;

R_2 represents a substituted or unsubstituted C_1-C_6 alkyl, cycloalkyl(C_1-C_6 alkyl)- or aryl(C_1-C_6 alkyl)- group;

and A represents a group of formula (IIA), or (IIB):



(IIA)

(IIB)

wherein R_4 represents the side chain of a natural or non-natural alpha amino acid, and R_5 and R_6 when taken together with the nitrogen atom to which they are attached form a saturated heterocyclic first ring of 5 to 7 atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 atoms; characterised in that

(a) the said second ring is substituted by $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_1$-$C_6)$alkoxy, hydroxy, mercapto, $(C_1$-$C_6)$alkylthio, halo, amino, trifluoromethyl, oxo, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a $(C_1$-$C_6)$alkyl group; and/or

(b) the said first or second ring is substituted by a group of formula (IIC), provided that the first ring is not substituted by phenoxy, benzyl or benzyl substituted by $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, phenoxy, hydroxy, mercapto, $(C_1$-$C_6)$alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a $(C_1$-$C_6)$alkyl group,

$$-(Alk^1)_m-(X)_p-(Alk^2)_n-Z \qquad \text{(IIC)}$$

wherein

m, p and n are independently 0 or 1;

Z represents, a hydroxy group, or a phenyl or heterocyclic ring of 5 to 7 atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 atoms

Alk^1 and Alk^2 independently represent divalent C_1-C_3 alkylene radicals;

X represents -O-, -S-, -S(O)-, -S(O_2)-, -C(=O)-, -NH-, -NR_7- where R_7 is C_1-C_3 alkyl;

<u>and wherein</u>

Alk^1, Alk^2 and Z when Z is not a hydroxy group independently are optionally substituted by

(C_1-C_6)alkyl, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl,
phenyl, or halophenyl,
trifluoromethyl,
monocyclic 5 or 6-membered hetrocyclic,
benzyl, or halophenylmethyl,
hydroxy, phenoxy, (C_1-C_6)alkoxy, or hydroxy(C_1-C_6)alkyl,
mercapto, (C_1-C_6)alkylthio or mercapto(C_1-C_6)alkyl,
oxo,
nitro,
cyano (-CN)
halo (bromo, chloro, fluoro, or iodo)
-COOH, or -$COOR^A$,
-$CONH_2$, -$CONHR^A$, or -$CONR^AR^B$
-COR^A, -SO_2R^A,
-$NHCOR^A$,
-NH_2, -NHR^A, or -NR^AR^B,

wherein R^A and R^B are independently a (C_1-C_6) alkyl group, R^A and R^B taken together with the nitrogen atom to which they are attached form a 5- or 6-

membered heterocyclic ring which may be substituted by (C_1C_3)alkyl, hydroxy, or hydroxy$(C_1\text{-}C_3)$alkyl.

A subset of compounds of the invention consists of those of formula (II) as defined above wherein :

(a) the said second ring is substituted by $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkoxy, hydroxy, mercapto, $(C_1\text{-}C_6)$alkylthio, amino, trifluoromethyl, oxo, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a $(C_1\text{-}C_6)$alkyl group; and/or

(b) the said first or second ring is substituted by a group of formula (IIC), provided that the first ring is not substituted by phenoxy, benzyl or benzyl substituted by $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, phenoxy, hydroxy, mercapto, $(C_1\text{-}C_6)$alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a $(C_1\text{-}C_6)$alkyl group,

$$-(Alk^1)_m-(X)_p-(Alk^2)_n-Z \qquad \text{(IIC)}$$

<u>wherein</u>

m, p and n are independently 0 or 1;

Z represents, a hydroxy group, or a phenyl or heterocyclic ring of 5 to 7 atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 atoms

Alk^1 and Alk^2 independently represent divalent $C_1\text{-}C_3$ alkylene radicals;

X represents -O-, -S-, -S(O)-, -S(O_2)-, -C(=O)-, -NH-, -NR_7- where R_7 is C_1-C_3 alkyl;

and wherein

Alk^1, Alk^2 and Z when Z is not a hydroxy group independently are optionally substituted by

(C_1-C_6)alkyl, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl,

phenyl, or halophenyl,

trifluoromethyl,

monocyclic 5 or 6-membered hetrocyclic,

benzyl,

hydroxy, phenoxy, or (C_1-C_6)alkoxy,

mercapto, or (C_1-C_6)alkylthio,

oxo,

nitro,

-COOH, or -$COOR^A$,

-$CONH_2$, -$CONHR^A$, or -$CONR^AR^B$

-COR^A,

-$NHCOR^A$,

-NH_2, -NHR^A, or -NR^AR^B,

wherein R^A and R^B are independently a (C_1-C_6) alkyl group,

In another aspect, the invention provides a method for the treatment of bacterial infections in humans and non-human mammals, which comprises administering to a subject suffering such infection an antibacterially effective dose of a compound of formula (II) as defined above.

In a further aspect of the invention there is provided a method for the treatment of bacterial contamination by applying an antibacterially effective amount of a compound of formula (II) as defined above to the site of contamination.

The compounds of formula (II) as defined above may be used as component(s) of

antibacterial cleaning or disinfecting materials.

On the hypothesis that the compounds (II) act by inhibition of intracellular PDF, the most potent antibacterial effect may be achieved by using compounds which efficiently pass through the bacterial cell wall. Thus, compounds which are highly active as inhibitors of PDF in vitro and which penetrate bacterial cells are preferred for use in accordance with the invention. It is to be expected that the antibacterial potency of compounds which are potent inhibitors of the PDF enzyme in vitro, but are poorly cell penetrant, may be improved by their use in the form of a prodrug, ie a structurally modified analogue which is converted to the parent molecule of formula (II), for example by enzymic action, after it has passed through the bacterial cell wall.

As used herein the term "$(C_1$-$C_6)$alkyl" means a straight or branched chain alkyl moiety having from 1 to 6 carbon atoms, including for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein the term "divalent $(C_1$-$C_3)$alkylene radical" means a saturated hydrocarbon chain having from 1 to 3 carbon atoms and two unsatisfied valencies.

As used herein the term "$(C_2$-$C_6)$alkenyl" means a straight or branched chain alkenyl moiety having from 2 to 6 carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. The term includes, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "C_2-C_6 alkynyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As used herein the term "cycloalkyl" means a saturated alicyclic moiety having from

3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the term "heteroaryl" refers to a 5- or 6- membered aromatic ring containing one or more heteroatoms;. Illustrative of such groups are thienyl, furyl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in particular means a 5-7 membered aromatic or non-aromatic heterocyclic ring containing one or more heteroatoms selected from S, N and O, including for example, pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, morpholinyl, benzofuranyl, pyranyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, maleimido and succinimido groups.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four substituents, each of which independently may be (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy, mercapto, (C_1-C_6)alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group

As used herein the terms "side chain of a natural alpha-amino acid" and "side chain of a non-natural alpha-amino acid" mean the group R^x in respectively a natural and non-natural amino acid of formula $NH_2-CH(R^x)-COOH$.

Examples of side chains of natural alpha amino acids include those of alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, histidine, 5-

hydroxylysine, 4-hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, α-aminoadipic acid, α-amino-n-butyric acid, 3,4-dihydroxyphenylalanine, homoserine, α-methylserine, ornithine, pipecolic acid, and thyroxine.

In natural alpha-amino acid side chains which contain functional substituents, for example amino, carboxyl, hydroxy, mercapto, guanidyl, imidazolyl, or indolyl groups as in arginine, lysine, glutamic acid, aspartic acid, tryptophan, histidine, serine, threonine, tyrosine, and cysteine, such functional substituents may optionally be protected.

Likewise, in the side chains of non-natural alpha amino acids which contain functional substituents, for example amino, carboxyl, hydroxy, mercapto, guanidyl, imidazolyl, or indolyl groups, such functional substituents may optionally be protected.

The term "protected" when used in relation to a functional substituent in a side chain of a natural or non-natural alpha-amino acid means a derivative of such a substituent which is substantially non-functional. The widely used handbook by T. W. Greene and P. G. Wuts "Protective Groups in Organic Synthesis" Second Edition, Wiley, New York, 1991 reviews the subject. For example, carboxyl groups may be esterified (for example as a C_1-C_6 alkyl ester), amino groups may be converted to amides (for example as a $NHCOC_1$-C_6 alkyl amide) or carbamates (for example as an $NHC(=O)OC_1$-C_6 alkyl or $NHC(=O)OCH_2Ph$ carbamate), hydroxyl groups may be converted to ethers (for example an OC_1-C_6 alkyl or a $O(C_1$-C_6 alkyl)phenyl ether) or esters (for example a $OC(=O)C_1$-C_6 alkyl ester) and thiol groups may be converted to thioethers (for example a tert-butyl or benzyl thioether) or thioesters (for example a $SC(=O)C_1$-C_6 alkyl thioester).

There are several actual or potential chiral centres in the compounds according to the invention because of the presence of asymmetric carbon atoms. The presence

of several asymmetric carbon atoms gives rise to a number of diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such diastereoisomers and mixtures thereof. Currently, the preferred stereoconfiguration of the carbon atom carrying the R_2 group is R; that of the carbon atom carrying the R_4 group (when asymmetric) is S; and that of the carbon atom carrying the R_1 group (when asymmetric) is R.

In the compounds of the invention:

R_1 may be, for example, hydrogen, methyl, or trifuoromethyl. Hydrogen is currently preferred.

R_2 may be, for example:

optionally substituted C_1-C_8 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl or cycloalkyl;

phenyl(C_1-C_6 alkyl)-, phenyl(C_3-C_6 alkenyl)- or phenyl(C_3-C_6 alkynyl)- optionally substituted in the phenyl ring;

cycloalkyl(C_1-C_6 alkyl)-, cycloalkyl(C_3-C_6 alkenyl)- or cycloalkyl(C_3-C_6 alkynyl)- optionally substituted in the cycloalkyl ring;

heterocyclyl(C_1-C_6 alkyl)-, heterocyclyl(C_3-C_6 alkenyl)- or heterocyclyl(C_3-C_6 alkynyl)- optionally substituted in the heterocyclyl ring; or

$CH_3(CH_2)_pO(CH_2)_q$- or $CH_3(CH_2)_pS(CH_2)_q$-, wherein p is 0, 1, 2 or 3 and q is 1, 2 or 3.

Specific examples of R_2 groups include

methyl, ethyl, n- and iso-propyl, n- and iso-butyl, n-pentyl, iso-pentyl 3-methyl-but-1-yl, n-hexyl, n-heptyl, n-acetyl, n-octyl, methylsulfanylethyl, ethylsulfanylmethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-ethoxymethyl, 3-

hydroxypropyl, allyl, 3-phenylprop-3-en-1-yl, prop-2-yn-1-yl, 3-phenylprop-2-yn-1-yl, 3-(2-chlorophenyl)prop-2-yn-1-yl, but-2-yn-1-yl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, furan-2-ylmethyl, furan-3-methyl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-2-ylmethyl, piperidinylmethyl, phenylpropyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, benzyl, 4-chlorobenzyl, 4-methylbenzyl, and 4-methoxybenzyl.

Presently preferred groups at R_2 are $(C_1\text{-}C_6)$alkyl-, cycloalkylmethyl-, $(C_1\text{-}C_3)$alkyl-S-$(C_1\text{-}C_3)$alkyl-, or $(C_1\text{-}C_3)$alkyl-O-$(C_1\text{-}C_3)$alkyl-, especially n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

R_4 may be, for example

the characterising group of a natural α amino acid, for example benzyl, or 4-methoxyphenylmethyl, in which any functional group may be protected, any amino group may be acylated and any carboxyl group present may be amidated; or

a group -$[Alk]_nR_9$ where Alk is a $(C_1\text{-}C_6)$alkylene or $(C_2\text{-}C_6)$alkenylene group optionally interrupted by one or more -O-, or -S- atoms or -$N(R_{12})$- groups [where R_{12} is a hydrogen atom or a $(C_1\text{-}C_6)$alkyl group], n is 0 or 1, and R_9 is hydrogen or an optionally substituted phenyl, aryl, heterocyclyl, cycloalkyl or cycloalkenyl group or (only when n is 1) R_9 may additionally be hydroxy, mercapto, $(C_1\text{-}C_6)$alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, -$CONH_2$, -$COOR^A$, -$NHCOR^A$, -$CONHR^A$, -NHR^A, -NR^AR^B, or -$CONR^AR^B$ wherein R^A and R^B are independently a $(C_1\text{-}C_6)$alkyl group; or

a benzyl group substituted in the phenyl ring by a group of formula -OCH_2COR_8 where R_8 is hydroxyl, amino, $(C_1\text{-}C_6)$alkoxy, phenyl$(C_1\text{-}C_6)$alkoxy,

$(C_1\text{-}C_6)$alkylamino, di($(C_1\text{-}C_6)$alkyl)amino, phenyl$(C_1\text{-}C_6)$alkylamino; or

a heterocyclic$(C_1\text{-}C_6)$alkyl group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, $(C_1\text{-}C_6)$alkoxy, cyano, $(C_1\text{-}C_6)$alkanoyl, trifluoromethyl $(C_1\text{-}C_6)$alkyl, hydroxy, formyl, amino, $(C_1\text{-}C_6)$alkylamino, di-$(C_1\text{-}C_6)$alkylamino, mercapto, $(C_1\text{-}C_6)$alkylthio, hydroxy$(C_1\text{-}C_6)$alkyl, mercapto$(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkylphenylmethyl; or

a group $-CR_aR_bR_c$ in which:

each of R_a, R_b and R_c is independently hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, phenyl$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl; or

R_c is hydrogen and R_a and R_b are independently phenyl or heteroaryl such as pyridyl; or

R_c is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, phenyl$(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_8)$cycloalkyl, and R_a and R_b together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

R_a, R_b and R_c together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

R_a and R_b are each independently $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, phenyl$(C_1\text{-}C_6)$alkyl, or a group as defined for R_c below other than hydrogen, or R_a and R_b together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and R_c is hydrogen, -OH, -SH, halogen, -CN, $-CO_2H$, $(C_1\text{-}C_4)$perfluoroalkyl, $-CH_2OH$, $-CO_2(C_1\text{-}C_6)$alkyl, $-O(C_1\text{-}C_6)$alkyl, $-O(C_2\text{-}C_6)$alkenyl, $-S(C_1\text{-}C_6)$alkyl, $-SO(C_1\text{-}C_6)$alkyl, $-SO_2(C_1\text{-}C_6)$ alkyl, $-S(C_2\text{-}C_6)$alkenyl, $-SO(C_2\text{-}C_6)$alkenyl, $-SO_2(C_2\text{-}C_6)$alkenyl or a group -Q-W wherein Q represents a

bond or -O-, -S-, -SO- or $-SO_2-$ and W represents a phenyl, phenylalkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkylalkyl, (C_4-C_8)cycloalkenyl, (C_4-C_8)cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, $-CO_2H$, $-CO_2(C_1-C_6)$alkyl, $-CONH_2$, $-CONH(C_1-C_6)$alkyl, $-CONH(C_1-C_6alkyl)_2$, -CHO, $-CH_2OH$, (C_1-C_4)perfluoroalkyl, $-O(C_1-C_6)$alkyl, $-S(C_1-C_6)$alkyl, $-SO(C_1-C_6)$alkyl, $-SO_2(C_1-C_6)$alkyl, $-NO_2$, $-NH_2$, $-NH(C_1-C_6)$alkyl, $-N((C_1-C_6)alkyl)_2$, $-NHCO(C_1-C_6)$alkyl, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, phenyl or benzyl.

Examples of particular R_4 groups include methyl, ethyl, benzyl, 4-chlorobenzyl, 4-hydroxybenzyl, phenyl, cyclohexyl, cyclohexylmethyl, pyridin-3-ylmethyl, tert-butoxymethyl, naphthylmethyl, iso-butyl, sec-butyl, tert-butyl, 1-benzylthio-1-methylethyl, 1-methylthio-1-methylethyl, 1-mercapto-1-methylethyl, 1-methoxy-1-methylethyl, 1-hydroxy-1-methylethyl, 1-fluoro-1-methylethyl, hydroxymethyl, 2-hydroxethyl, 2-carboxyethyl, 2-methylcarbamoylethyl, 2-carbamoylethyl, and 4-aminobutyl. Presently preferred R_4 groups include tert-butyl, iso-butyl, benzyl, isopropyl and methyl.

R_5 and R_6 taken together with the nitrogen atom to which they are attached form a saturated 5- to 7-membered monocyclic N-heterocyclic first ring which is attached via the N atom, and which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 atoms. One or more additional ring hetero atoms such as nitrogen may be present in the first ring. Examples of such first rings are 1-pyrrolidinyl, piperidin-1-yl, 1-piperazinyl, hexahydro-1-pyridazinyl, morpholin-4-yl, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-thiazin-4-yl 1-oxide, tetrahydro-1,4-thiazin-4-yl 1,1-dioxide, hexahydroazipino, thiomorpholino, diazepino, thiazolidinyl or octahydroazocino. Presently preferred are piperidin-1-yl and 1-piperazinyl. The substituent (IIC) may be present on a ring carbon atom or a ring nitrogen atom of the first or second rings.

In the substituent (IIC) (from whose definition benzyl, certain substituted benzyls, and phenoxy are excluded) Alk^1 and Alk^2 may independently represent, for example -(CH_2)- or -(CH_2CH_2)-. In the case where m is 0 and p is 1, X may be, for example -C(=O)- or -S(O_2)-. In such cases n may be 0 or 1, and when the -NR_5R_6 first ring contains a second ring nitrogen, the -C(=O)- or -S(O_2)- of (IIC) may be linked to that ring nitrogen in an amide or sulphonamide bond.

In the substituent (IIC) m, n and p may all be 0, so that the group Z is directly linked to the -NR_5R_6 first ring.

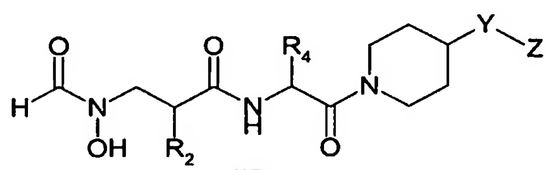
In a preferred subset of the compounds of the invention, the substituent (IIC) has the formula -CH_2Z, -OZ, or -(C=O)Z wherein (subject to the exclusion of benzyl, certain substituted benzyls, and phenoxy) Z is a phenyl, 3,4-methylenedioxyphenyl, morpholinyl, pyrimidinyl, 1,2,3-thiadiazolyl, 1,4-thiazolyl, benzofuranyl, furanyl, thienyl, pyranyl, pyrrolyl, pyrazolyl, isoxazolyl, or pyridyl ring which may optionally be substituted as specified. In particular, Z may be a phenyl, 3,4-methylenedioxyphenyl, morpholinyl, pyrimidin-2-yl, 1,2,3-thiadiazol-5-yl, 1,4-thiazol-5-yl, benzofuran-2-yl, 2- or 3-furanyl, 2- or 3-thienyl, 2- or 3-pyranyl, 2-, 3- or 4-pyrrolyl, 3-, 4- or 5-pyazolyl, 3-, 4- or 5-isoxazolyl, or 2-, 3- or 4-pyridyl ring any of which may optionally be substituted as specified in the broad description of the compounds of the invention.

In the compounds of formula (II) as defined above wherein Q is a radical of formula -C(=O)NH(OH) the radicals R_1, R_2, and A may be any of those discussed ubove in relation to compounds (II) wherein Q is a radical of formula -N(OH)CH(=O). However, in addition, R_1 may be, for example, a hydroxy, methoxy, ethoxy, n-propyloxy, allyloxy, amino, methylamino, dimethylamino, ethylamino, or diethylamino group.

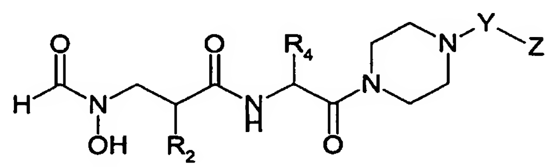
Specific examples of substituents (IIC) include those present in the compounds specifically named, and/or exemplified herein.

Examples of specific compounds of the invention are those of the Examples herein. In those Examples, where a compound of formula (II) above wherein Q is an N-formylhydroxylamine radical -N(OH)CH(=O) is disclosed, it is to be understood that the equivalent compound wherein Q is a hydroxamate radical -C(=O)NH(OH) is also a specific compound of the invention, and *vice versa*.

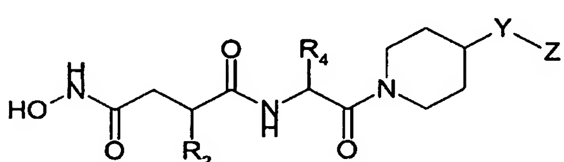
Preferred compounds of the invention include those selected from the group consisting of compounds of formulae (IID) - (IIG) and (IIW) - (IIZ):



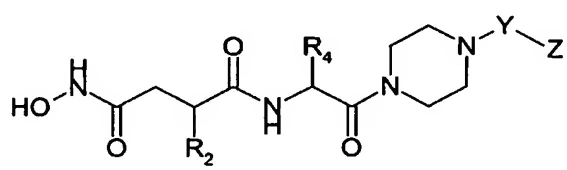
(IID)



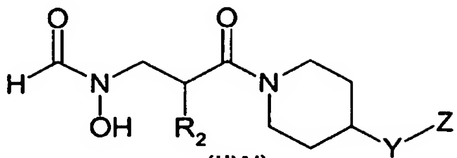
(IIE)



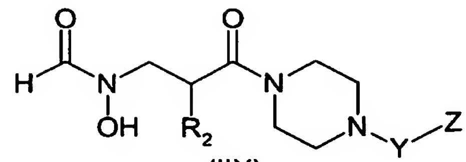
(IIF)



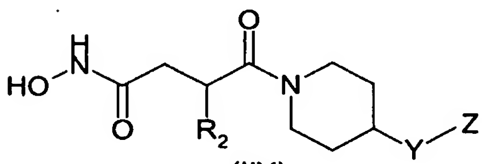
(IIG)



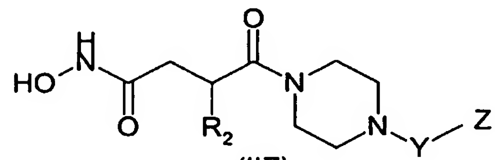
(IIW)



(IIX)



(IIY)



(IIZ)

wherein

R_2 is n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl;

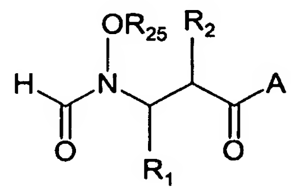
R_4 is tert-butyl, iso-butyl, benzyl or methyl;

Y is $-CH_2-$, -O- or -(C=O)-; and

Z is a phenyl, 3,4-methylenedioxyphenyl, morpholinyl, pyrimidinyl, 1,2,3-thiadiazolyl, 1,4-thiazolyl, benzofuranyl, furanyl, thienyl, pyranyl, pyrrolyl, pyrazolyl, isoxazolyl, or pyridyl ring; in particular, a phenyl, 3,4-methylenedioxyphenyl, morpholinyl, pyrimidin-2-yl, 1,2,3-thiadiazol-5-yl, 1,4-thiazol-5-yl, benzofuran-2-yl, 2-or 3-furanyl, 2- or 3-thienyl, 2- or 3-pyranyl, 2-, 3- or 4-pyrrolyl, 3-, 4- or 5-pyazolyl, 3-, 4- or 5-isoxazolyl, or 2-, 3- or 4-pyridyl ring, which may optionally be substituted as specified in the general description of compounds of the invention.

Particular compounds of the invention, preferred for their potency against organisms which infect the respiratory system, include *N*-[1*S*-(4-benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-2*R*-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide and *N*-[1*S*-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-2*R*-cyclopentylmethyl-*N*-hydroxy-succinamide

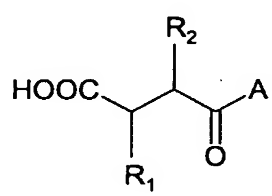
Compounds of the invention in which Q is an N-formylhydroxyamino group may be prepared by deprotecting an O-protected N-formyl-N-hydroxyamino compound of formula (III):



(III)

in which R_1, R_2, and A are as defined in general formula (I) and R_{25} is a hydroxy protecting group removable to leave a hydroxy group by hydrogenolysis or hydrolysis. Benzyl is a preferred R_{25} group for removal by hydrogenolysis, and tert-butyl and tetrahydropyranyl are preferred groups for removal by acid hydrolysis.

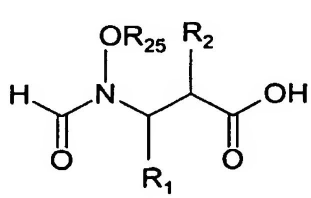
Compounds of the invention in which Q is a hydroxamic acid group may be prepared by reacting the parent compound wherein Q is a carboxylic acid group (IIIA)



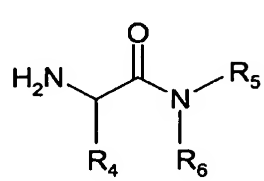
(IIIA)

with hydroxylamine or an N- and/or O-protected hydroxylamine, and thereafter removing any O- or N-protecting groups

Compounds of formula (III) or (IIIA) may be prepared by causing an acid of formula (IV) or (IVC) or an activated derivative thereof to react with an amine of formula (IVA) or (IVB)



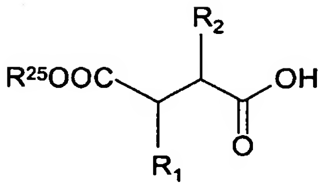
(IV)



(IVA)

HNR_5R_6

(IVB)

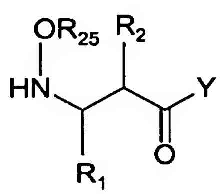


(IVC)

wherein R_1 R_2, R_4, R_5, and R_6 are as defined in general formula (II) except that any substituents in R_1 R_2, R_4, R_5, and R_6 which are potentially reactive in the coupling reaction may themselves be protected from such reaction, and R_{25} is as defined in relation to formula (III) above, and optionally removing protecting groups R_1, R_2, R_4, R_5, and R_6.

Compounds of formula (IVA), (IVB) and (IVC) are prepared by standard literature methods, and many are commercially available.

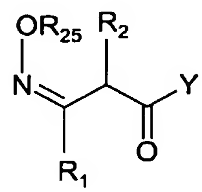
Compounds of formula (IV) may be prepared by N-formylation, for example using acetic anhydride and formic acid, or 1-formylbenzotriazole, of compounds of formula (V)



(V)

wherein R_1, R_2 and R_{25} are as defined in relation to formula (III) and Y is either a chiral auxiliary or an OR_{26} group wherein R_{26} is hydrogen or a hydroxy protecting group. In the case where Y is an OR_{26} group or a chiral auxiliary the hydroxy protecting group or auxiliary is removed after the formylation step to provide the compound of formula (IV). Suitable chiral auxiliaries include substituted oxazolidinones which may be removed by hydrolysis in the presence of base.

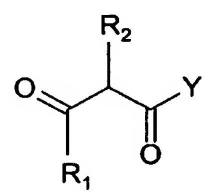
A compound of general formula (V) may be prepared by reduction of an oxime of general formula (VII)



(VII)

wherein R_1, R_2, and R_{25} are as defined above, and Y is either an OR_{26} group as defined above or a chiral auxiliary. Reducing agents include certain metal hydrides (eg sodium cyanoborohydride in acetic acid, triethylsilane or borane/pyridine) and hydrogen in the presence of a suitable catalyst. Following the reduction when the group Y is a chiral auxiliary it may be optionally converted to a OR_{26} group.

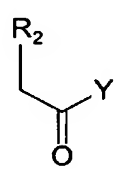
A compound of general formula (VII) can be prepared by reaction of a β-keto carbonyl compound of general formula (VIII)



(VIII)

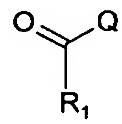
wherein R_1, R_2, and Y are as defined above, with an O-protected hydroxylamine.

β-keto carbonyl compounds (VIII) may be prepared in racemic form by formylation or acylation of a carbonyl compound of general formula (IX)



(IX)

wherein R_2 and Y are as defined above, with a compound of general formula (X)



(X)

wherein R_1 is as defined above and Q is a leaving group such as halogen or alkoxy, in the presence of a base.

The Examples herein provide further details of routes and methods for the preparation of compounds of the invention.

Salts of the compounds of the invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane sulphonates, p-toluenesulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates. Salts may also be formed with bases, for example sodium, potassium, magnesium, and calcium salts.

Compositions with which the invention is concerned may be prepared for administration by any route consistent with the pharmacokinetic properties of the active ingredient(s).

Orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral

liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Safe and effective dosages for different classes of patient and for different disease states will be determined by clinical trial as is required in the art. It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following examples illustrate embodiments of the invention. Note that the "Preparative Example A" does not describe the preparation of a compound of the invention, but is included to provide details of synthetic routes and methods for the preparation of compounds of the invention

^{1}H and ^{13}C NMR spectra were recorded using a Bruker DPX 250 spectrometer at 250.1 and 62.9MHz, respectively. Mass spectra were obtained using a Perkin Elmer Sciex API 165 spectrometer using both positive and negative ionisation modes. Infra-red spectra were recorded on a Perkin Elmer PE 1600 FTIR spectrometer. Analytical HPLC was performed on a Beckman System Gold, using Waters Nova Pak C18 column (150 mm, 3.9 mm) with 20 to 90 % solvent B gradient (1 ml/min) as the mobile phase. [Solvent A: 0.05% TFA in 10% water 90% methanol; Solvent B:

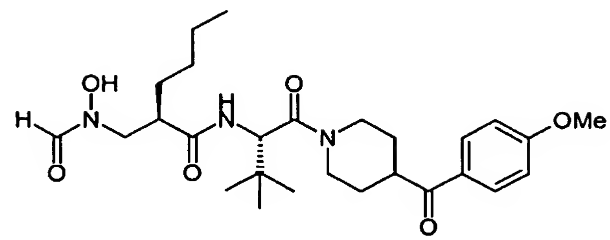
0.05% TFA in 10% methanol 90%], detection wavelength at 230 nm. Preparative HPLC was performed on a Gilson autoprep instrument using a C18 Waters delta prep-pak cartridge (15µm, 300 A, 25 mm, 10 mm) with 20 to 90 % solvent B gradient (6 ml/min) as the mobile phase. [Solvent A water; Solvent B: methanol], UV detection was at 230 nm.

The following abbreviations have been used throughout:

DCM	Dichloromethane
DEAD	Diethyl-azo-dichlorocarboxylate
EDC	N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride
HOAt	1-Hydroxy-7-aza-benzotriazole
HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
LRMS	Low resolution mass spectrometry
NMR	Nuclear magnetic resonance
RT	Retention Time
TLC	Thin layer chromatography
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

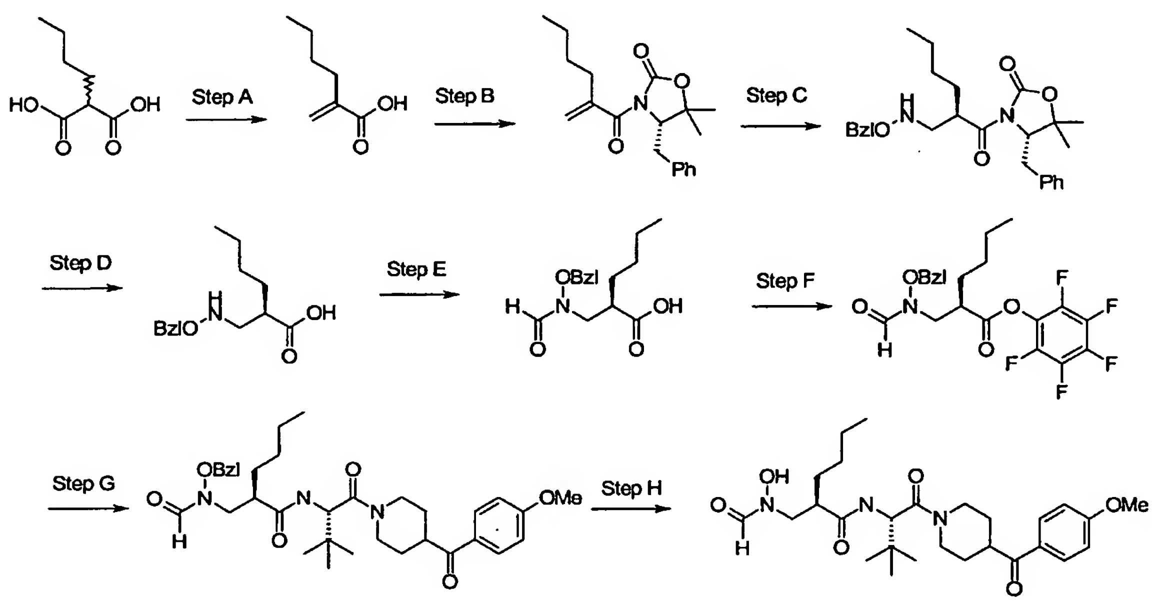
Example 1

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1S-[4-(4-methoxy-benzoyl)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-amide



The title compound was prepared as detailed below (see also Scheme 1)

Scheme 1



Reagents and conditions: A. piperidine, HCHO, EtOH,80°C, O/N; B. ^{t}BuCOCl, Et_3N then 3-lithio-4-benzyl-5,5-dimethyl-oxazolidin-2-one; C. H_2NOBzl, room temp., O/N then pTsOH, EtOAc; D. LiOH, aq. THF, 0°C; E. formic acetic anhydride, Et_3N, THF; F. PfpOH, EDC, HOBt, THF; G. amine, CH_2Cl_2; H. cyclohexene, Pd/C, EtOH.

Step A: 2-Butyl acrylic acid

To a solution of n-butylmalonic acid (17.2 g, 107 mmol) in ethanol (200 ml) was added piperidine (12.76 ml, 129 mmol) and 37% aq. formaldehyde (40.3 ml, 538 mmol). The

solution was heated to 80 °C during which time a precipitate appeared and gradually redissolved over 1 hour. The reaction mixture was stirred at 80 °C overnight then cooled to room temperature. The solvents were removed under reduced pressure and the residue was dissolved in ethyl acetate (200 ml), washed successively with 1 M hydrochloric acid and brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated to give the title compound as a clear oil (13.37 g, 97%). ^{1}H-NMR; δ ($CDCl_3$), 6.29 (1H, s), 5.65 (1H, s), 2.34-2.28 (2H, m), 1.54-1.26 (4H, m), 0.94 (3H, t, J = 7.1 Hz).

Step B: 4S-Benzyl-3-(2-butyl-acryloyl)-5,5-dimethyl-oxazolidin-2-one

2-Butyl acrylic acid (21.5 g, 168 mmol) was dissolved in dry THF (500 ml) and cooled to -78 °C under a blanket of argon. Triethylamine (30 ml, 218 mmol) and pivaloyl chloride (21 ml, 168 mmol) were added at such a rate that the temperature remained below -60 °C. The mixture was stirred at -78 °C for 30 minutes, warmed to room temperature for 2 hours and finally cooled back to -78 °C.

In a separate flask, 4S-benzyl-5,5-dimethyl-oxazolidin-2-one was dissoved in dry THF (500ml) and cooled to -78 °C under a blanket of argon. n-Butyllithium (2.4 M solution in hexanes, 83 ml, 200 mmol) was added slowly and the mixture was stirred for 30 minutes at room temperature. The resulting anion was tranferred *via* a cannula into the original reaction vessel. The mixture was allowed to warm to room temperature and was stirred overnight at room temperature. The reaction was quenched with 1 M potassium hydrogen carbonate (200 ml) and the solvents were removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give an orange oil. TLC analysis revealed the presence of unreacted chiral auxiliary in addition to the required product. A portion of the material (30 g) was dissolved in dichloromethane and flushed through a silica pad to give pure title compound as a yellow oil (25.3 g). ^{1}H-NMR; δ ($CDCl_3$), 7.31-7.19 (5H, m), 5.41 (2H,s), 4.51 (1H, dd, J = 9.7 & 4.2 Hz), 3.32 (1H, dd, J = 14.2 & 4.2 Hz), 2.82

(1H, dd, J = 14.2 & 9.7 Hz), 2.40-2.34 (2H, m), 1.48-1.32 (4H, m), 1.43 (3H, s), 1.27 (3H, s), 0.91 (3H, t, J = 7.1 Hz). Some chiral auxiliary was recovered by flushing the silica pad with methanol.

Step C: 4S-Benzyl-3-[2-(benzyloxyamino-methyl)-hexanoyl]-5,5-dimethyl-oxazolidin-2-one (p-toluenesulfonic acid salt)

4S-Benzyl-3-(2-butyl-acryloyl)-5,5-dimethyl-oxazolidin-2-one (19.8 g, 62.8 mmol) was mixed with O-benzylhydroxylamine (15.4 g, 126 mmol) and stirred overnight at room temperature. The mixture was dissolved in ethyl acetate and the solution was washed with 1 M hydrochloric acid, 1 M sodium carbonate and brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford a pale yellow oil (25.3 g) which was shown by NMR and HPLC analysis to contain 4S-benzyl-3-[2-(benzyloxyamino-methyl)-hexanoyl]-5,5-dimethyl-oxazolidin-2-one (ca. 82% d.e.) along with a trace of starting material. The product was combined with another batch (26.9g, 76% d.e.) and dissolved in ethyl acetate (200 ml). p-Toluenesulfonic acid (22.7 g, 119 mmol) was added and the mixture was cooled to 0 °C. The title compound was obtained as a white crystalline solid by seeding and scratching. Yield: 25.2g, (34%, single diastereoisomer). A second crop (14.7 g, 20%, single diastereoisomer) was also obtained. ^{1}H-NMR;δ ($CDCl_3$), 7.89 (2H, d, J = 8.2 Hz), 7.37-7.12 (10H, m), 7.02 (2H, d, J = 6.9 Hz), 5.28-5.19 (2H, m), 4.55 (1H, m), 4.23 (1H, m), 3.93 (1H, m), 3.58 (1H, m), 2.58 (1H, m), 2.35 (3H, s), 1.67-1.51 (2H, m), 1.29-1.16 (4H, m), 1.25 (3H, s), 1.11 (3H, s), 0.80-0.75 (3H, m).

Step D: 2R-(Benzyloxyamino-methyl)-hexanoic acid

4S-Benzyl-3-[2R-(benzyloxyamino-methyl)-hexanoyl]-5,5-dimethyl-oxazolidin-2-one p-toluenesulfonic acid salt (25.2 g, 40.2 mmol) was partitioned between ethyl acetate and 1 M sodium carbonate. The organic phase was dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residual oil was dissolved in THF (150 ml) and water (50 ml), cooled to 0 °C and treated with lithium hydroxide

(1.86 g, 44.2 mmol). The solution was stirred for 30 minutes at 0 °C, then overnight at room temperature. The reaction was acidified to pH4 with 1 M citric acid and the solvents were removed. The residue was partitioned between dichloromethane and 1 M sodium carbonate. The basic aqueous layer was acidified to pH4 with 1M citric acid and extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated to provide the title compound as a colourless oil (7.4 g, 73%). ^{1}H-NMR;δ ($CDCl_3$), 8.42 (2H, br s), 7.34-7.25 (5H, m), 4.76-4.66 (2H, m), 3.20-3.01 (2H, m), 2.73 (1H, m), 1.70-1.44 (2H, m), 1.34-1.22 (4H, m) and 0.92-0.86 (3H, m).

Step E: 2R-[(Benzyloxy-formylamino)-methyl)]-hexanoic acid

To a solution of 2R-(Benzyloxyamino-methyl)-hexanoic acid (30.6 g, 0.12 mol) in dry THF (300 ml) was added formic acetic anhydride (26.8 ml, 0.31 mol) at 0°C. Triethylamine (18.5 ml, 0.13 mol) was added and the reaction was stirred for 1 h at 0 °C and 60 h at room temperature. The solvent was removed *in vacuo* to yield the title compound as a yellow oil (33.6 g, 99%) which was used in Step F without further purification. ^{1}H-NMR; ($CDCl_3$, rotamers), 8.20-8.08 (0.7H, br s), 8.07-7.92 (0.3H, br s), 7.50-7.25 (5H, br m), 5.07-4.70 (2H, br m), 3.95-3.52 (2H, br m), 2.90-2.66 (1H, br s), 1.72-1.20 (6H, br m), 1.00-0.78 (3H, br s). LRMS: +ve ion 280 [M+1].

Step F: 2R-[(Benzyloxy-formyl-amino)-methyl]-hexanoic acid pentafluoro-phenyl ester

To a solution of 2R-[(Benzyloxy-formylamino)-methyl)]-hexanoic acid (7.8 g, 19.9 mmol) in dry THF (500 ml) was added pentafluorophenol (44.3 g, 0.24 mol), EDC (27.7 g, 0.14 mol) and HOBt (16.2 g, 0.12 mol). The reaction was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate, washed successively with 1 M sodium carbonate (3 x 500 ml) and water (1 x 500 ml), dried over anhydrous magnesium sulfate and filtered. The solvent was removed *in vacuo* to yield a yellow oil (60 g) that was purified by flash chromatography

(5:1, hexane:ethyl acetate → 1:2 hexane:ethyl acetate) to yield a clear oil (42.0 g, 79%). ^{1}H-NMR; δ($CDCl_3$, rotamers), 8.20-8.09 (0.7H, br s), 8.09-7.92 (0.3H, br s), 7.60-7.21 (5H, br m), 5.00-4.70 (2H, br m), 4.04-3.72 (2H, br m), 3.18-3.00 (1H, br s), 1.85-1.57 (2H, br m), 1.50-1.26 (4H, br m), 1.00-0.82 (3H, br m); LRMS: 466 [M+H].

Step G: 2R-[(Benzyloxy-formyl-amino)-methyl]-hexanoic acid {1S-[4-(4-methoxy-benzoyl)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-amide

2R-[(Benzyloxy-formyl-amino)-methyl]-hexanoic acid pentafluorophenyl ester (231mg, 0.52mmol) and 2S-amino-1-[4-(4-methoxy-benzoyl)-piperidin-1-yl]-3,3-dimethyl-butan-1-one (prepared fromr N-benzyloxycarbonyl-L-tert-leucine) (259 mg, 0.78mmol) were dissolved in dichloromethane (6ml) and the mixture was stirred overnight at 27°C. An excess of Amberlyst A-21 ion exchange resin was added and the mixture stirred for 2.5hrs before filtration. The resulting solution was then treated with methyl isocyanate polystyrene resin for 5hrs. The mixture was filtered and solvent was removed under reduced pressure. Mass spectrometric analysis showed presence of pentafluorophenol, so the residue was dissolved in methanol (5ml) and an excess of A-26 carbonate resin was added. The mixture was stirred overnight before filtration and removal of solvent under reduced pressure to afford the title compound as a brown oil (358 mg, 0.60mmol). LRMS: +ve ion 594 [M+H].

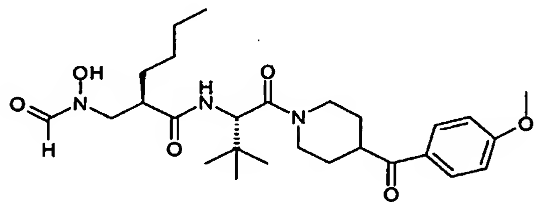
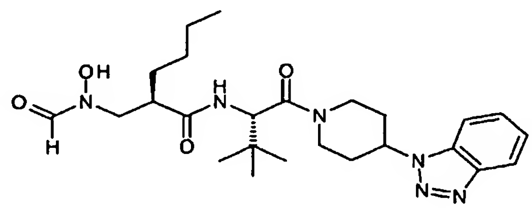
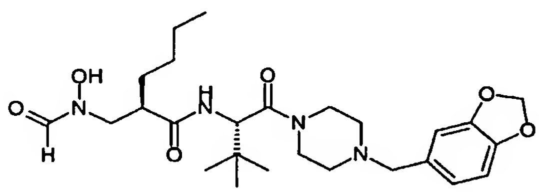
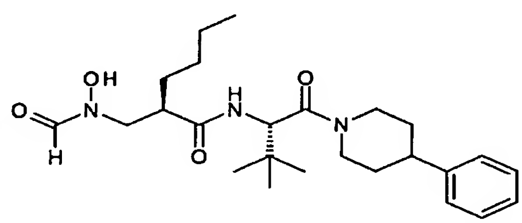
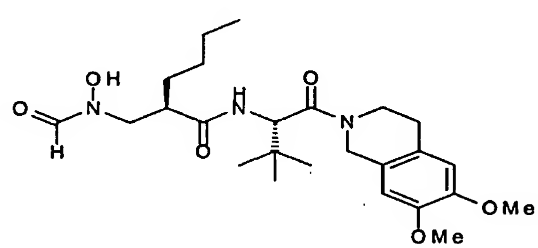
Step H: 2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1S-[4-(4-methoxy-benzoyl)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-amide

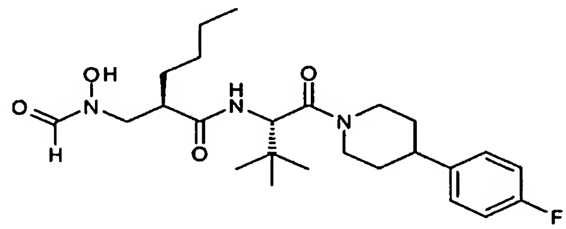
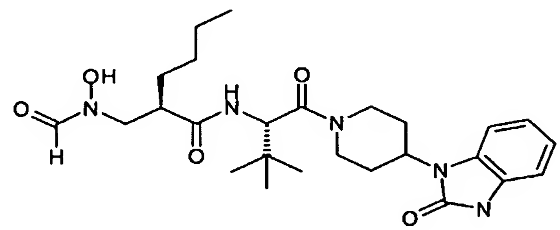
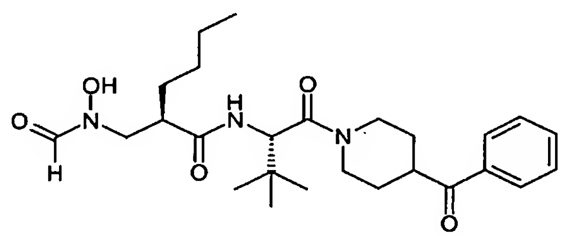
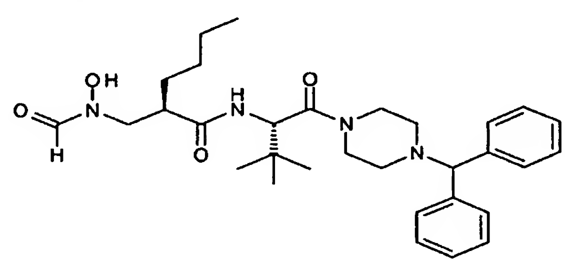
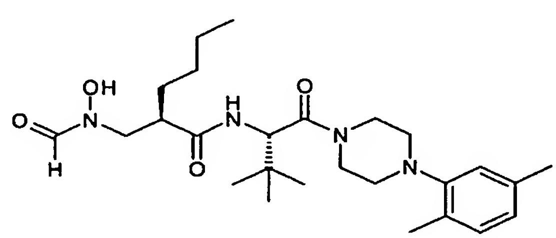
2R-[(Benzyloxy-formyl-amino)-methyl]-hexanoic acid {1S-[4-(4-methoxy-benzoyl)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-amide (358mg, 0.60 mmol) was dissolved in ethanol (6 ml). Cyclohexene (0.60ml) was added and the mixture placed under a blanket of argon. A suspension of 10% palladium on charcoal (40mg) in ethyl acetate (1 ml) was added and the mixture was stirred at 70°C for 5hrs. The reaction mixture was cooled and the catalyst removed by filtration. The filtrate was concentrated to provide the title compound as a brown oil (294mg, 0.58mmol). Characterising data are

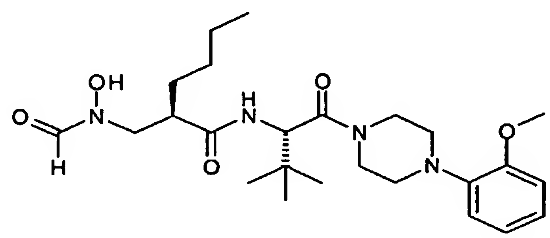
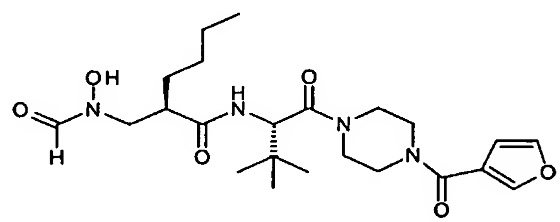
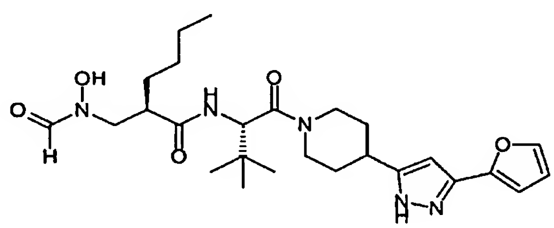
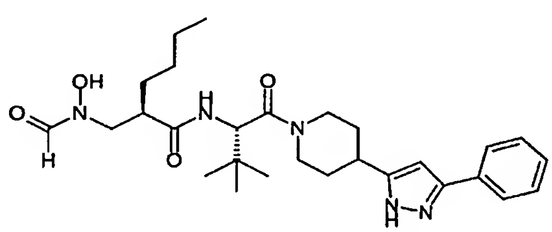
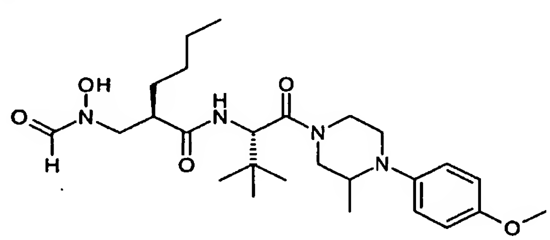
provided in Table 1.

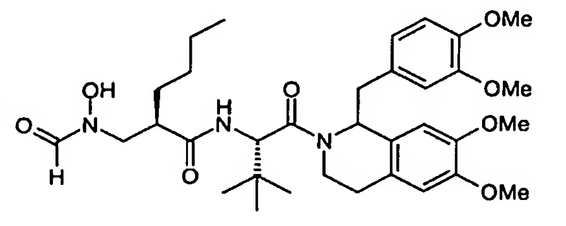
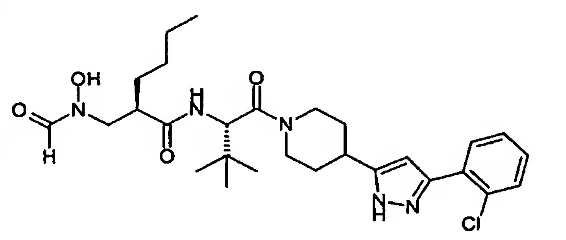
The compounds of Examples 2-13 were prepared by the synthetic route outlined in Scheme 1 and as described in detail for Example 1. Steps G and H were carried out in parallel for all examples. L-*tert*-leucine derivatives were prepared according to established literature methods. Purification of the final compounds, where necessary, was carried out by preparative HPLC.

Table 1

Example	Structure	Mass Spec. Data	HPLC
1		[M+H]=504	RT=21.7mins 88% pure
2		[M+H]=487	RT=20.1mins 85% pure
3		[M+H]=505 [M-H]=503	RT=17.3mins 83% pure
4		[M+H]=447 [M-H]=445	RT=21.5mins 90% pure
5		[M+H]=478 [M+Na]=500 [M-H]=476	RT=20.8mins 95% pure

6		[M+H]=465 [M-H]=463	RT=20.6mins 93% pure
7		[M+H]=502 [M+Na]=524 [M-H]=500	RT=19.3mins 94% pure
8		[M+Na]=496 [M-H]=472	RT=21.2mins 91% pure
9		[M+H]=537 [M-H]=535	RT=19.8mins 95% pure
10		[M+H]=475 [M-H]=473	RT=24.3mins 87% pure

11		[M+H]=477 [M-H]=475	RT=20.3mins 84% pure
12		[M+Na]=487 [M-H]=463	RT=18.7mins 94% pure
13		[M+H]=502	RT=21.0mins 88% pure
14		[M+H]=512 [M-H]=510	RT=21.7mins 84% pure
15		[M+H]=491 [M-H]=489	RT=18.7mins 98% pure

16		[M+Na]=650 [M-H]=626	RT=21.5mins 86% pure
17#		[M+H]=546 [M-H]=544	RT=22.8mins 88% pure

^{1}H-NMR; δ (CD_3OD, rotamers), 8.26 (0.4H, s), 7.84 (0.6H, s), 7.69 (2H, m), 7.39 (2H, m), 6.49 (0.4H, s), 6.42 (0.6H, s), 5.01 (0.6H, s), 4.96 (0.4H, s), 4.64 (0.6H, d, J=13.1 Hz), 4.51 (0.4H, d, J=13.2 Hz), 4.36 (0.6H, d, J=13.2 Hz), 4.29 (0.4H, d, J=13.6 Hz), 3.10 (1H, m), 3.43 (0.4H, m), 3.32 (0.6H, m), 3.00 (2H, m), 2.86 (2H, m), 2.09 (2H, m), 1.59 (4H, m), 1.27 (4H, m), 1.02 (9H, m), 0.90 (1.4H, s) and 0.79 (1.6H, s).

The compounds of Examples 18 to 40 were prepared from 2R-[(Benzyloxy-formyl-amino)-methyl]-hexanoic acid pentafluorophenyl ester in a similar way to Example 1 but with the following modifications.

Step G: Generic experimental procedure for the synthesis of an array of amides

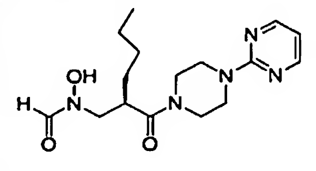
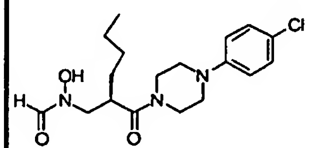
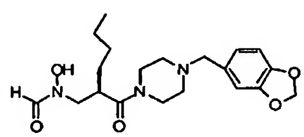
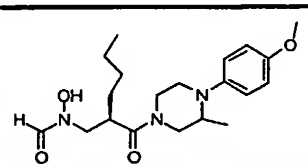
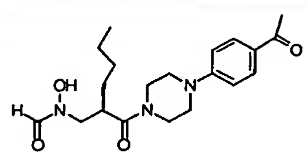
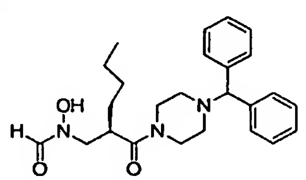
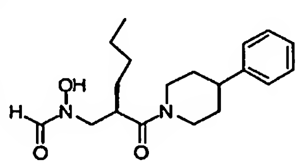
The coupling of amines to the pentafluorophenyl ester were carried out on a Zymate XPII laboratory robot. To a solution of the pentafluorophenyl ester (55.8 mg, 0.12 mmol) in dichoromethane (2 ml) were added the individual amines (0.25 mmol) and the reaction mixtures were stirred at room temperature for 60 h. Purification was effected by removing excess amine and pentafluorophenol using scavenger resins. The pentafluorophenol was removed using a three fold excess (0.36 mmol) of A-26 carbonate resin (3.5 mmol loading). The resin was added to the reaction mixtures and

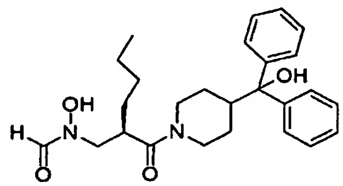
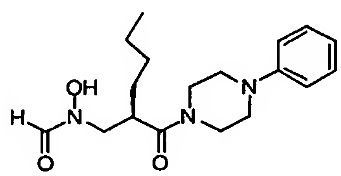
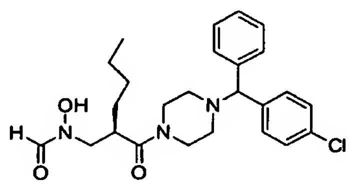
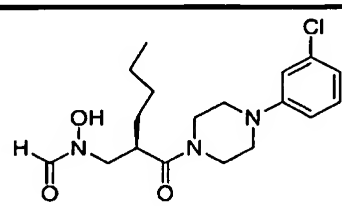
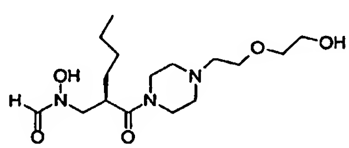
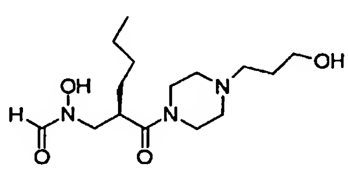
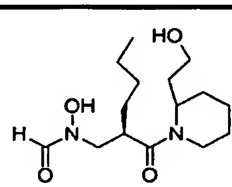
agitated for 24 h, after which time it was filtered off. The excess amines were removed using a three fold excess (0.36 mmol) of methylisocyanate polystyrene resin (1.2 mmol loading). The resin was added to the reaction mixtures and agitated for 4 h, after which time it was filtered off. The solvent was removed *in vacuo* using a Savant Speed Vac Plus to yield the coupled products. Yields were not calculated and the purity and integrity of each compound was verified using HPLC and LRMS.

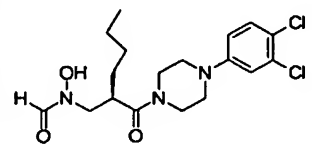
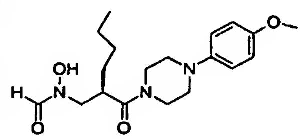
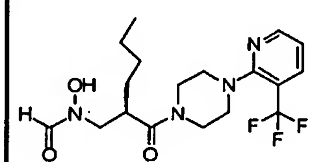
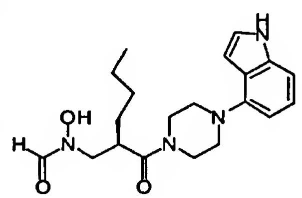
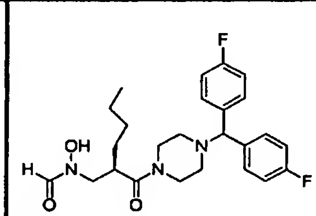
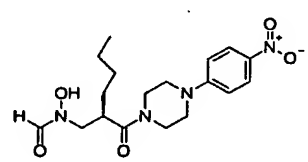
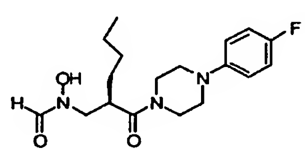
Step H: Generic Transfer Hydrogenation Procedure

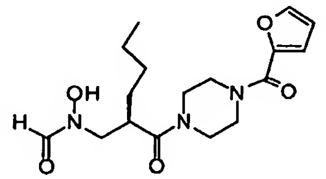
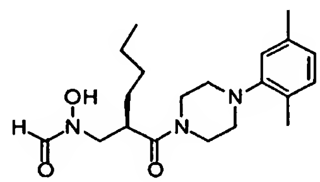
Coupled products from Step G were taken up in an ethanol-cyclohexene solution (3 ml, 10% in cyclohexene) and Pd/C (20% w/w) was added and the reactions stirred at 80 °C for 24 h. The Pd/C was filtered off and the solvent was removed *in vacuo* using a Savant Speed Vac Plus to yield the title compounds (Examples 18 to 40, Table 2). Yields were not calculated and the purity and integrity of each compound was verified using HPLC and LRMS.

Table 2

Example	Structure	Mass Spectral Data	HPLC	Purification
18		336 (M+1, 70)	RT 7.5 min 100%	Ion exchange resin, Prep HPLC
19		368 (M+1, 100)	RT 21.8 min 80%	Resins, Prep HPLC
20		392 (M+1, 100)	RT 8.2 min 100%	Resins Prep HPLC
21		378(M+1, 40) 362([M+1]-Me, 100)	RT 12.0 min and 12.2 min (diastereomers) >98%	Resins Prep HPLC
22		376 (M+1, 100)	RT 18.5 min 100%	Resins
23		424 (M+1, 30), 258 ([M+1]-$[C_6H_5]_2CH$, 100)	RT 17.5 min 95%	Resins
24		333 (M+1, 30)	RT 21.6 min 100%	Resins

25		421 (M+1-H_2O, 50) 437 (M-1, 60)	RT 22.3 min 100%	Resins prep HPLC
26		334 (M+1, 100)	RT 17.7 min 100%	Resins
27		458 (M+1, 20) 258 ([M+1]- [C_6H_5]C_6H_4ClCH, 100)	RT 26.4 min 100%	Resins prep HPLC
28		368 (M+1, 100)	RT 22.1 min 100%	Resins prep HPLC
29		346 (M+1, 100)	2 peaks, RT 3.2 min and 3.6 min 100%	Resins
30		316 (M+1, 100)	2 peaks, RT 3.1 min and 3.5 min 100%	Resins
31		283([M+1]-H_2O, 90)	1 peak with shoulder, RT 16.8 min	Resins

32		402 (M+1, 100)	RT 15.8 min >95%	Resins
33		364 (M+1, 100)	RT 11.7 min >95%	Resins
34		403 (M+1, 100)	RT 14.7 min 95%	Resins
35		373 (M+1, 100)	RT 14.5 min 95%	Resins
36		460 (M+1, 100)	RT 13.3 min >95%	Resins, Prep HPLC
37		379 (M+1, 100),	RT 13.6 min >95%	Resins
38		352 (M+1, 100)	RT 5.9 min > 95%	Resins

39		352 (M+1, 100)	RT 11.3 min >95%	Resins
40		362 (M+1, 100)	15.7 min >95%	Resins

The compounds of the Examples 1-40 are named as follows:

Example 1
2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid
51{1S-[4-(4-methoxy-benzoyl)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 2
2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid
[1S-(4-benzotriazol-1-yl-piperidine-1-carbonyl)-2,2-dimethyl-propyl]-amide

Example 3
2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid
[1S-(4-benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-amide

Example 4
2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid
[2,2-dimethyl-1S-(4-phenyl-piperidine-1-carbonyl)-propyl]-amide

Example 5

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinoline-2-carbonyl)-2,2-dimethyl-propyl]-amide

Example 6

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1S-[4-(4-fluoro-phenyl)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 7

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1S-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-propyl}-amide

Example 8

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(4-benzoyl-piperidine-1-carbonyl)-2,2-dimethyl-propyl]-amide

Example 9

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(4-benzhydryl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-amide

Example 10

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1S-[4-(2,5-dimethyl-phenyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 11

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1S-[4-(2-methoxy-phenyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 12

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1S-[4-(furan-3-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 13

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1S-[4-(5-furan-2-yl-2*H*-pyrazol-3-yl)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 14

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1S-[4-(5-phenyl-2*H*-pyrazol-3-yl)-piperidine-1-carbonyl]-propyl}-amide

Example 15

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1S-[4-(4-methoxy-phenyl)-3-methyl-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 16

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1S-[1-(3,4-dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinoline-2-carbonyl]-2,2-dimethyl-propyl}-amide

Example 17

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid (1S-{4-[5-(2-chloro-phenyl)-2*H*-pyrazol-3-yl]-piperidine-1-carbonyl}-2,2-dimethyl-propyl)-amide

Example 18

N-Hydroxy-N-[2R-(4-pyrimidin-2-yl-piperazine-1-carbonyl)-hexyl]-formamide

Example 19

N-{2R-[4-(4-Chloro-phenyl)-piperazine-1-carbonyl]-hexyl}-N-hydroxy-formamide

Example 20

N-[2R-(4-benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carbonyl)-hexyl]-N-hydroxy-formamide

Example 21

N-Hydroxy-N-{2R-[4-(4-methoxy-phenyl)-3-methyl-piperazine-1-carbonyl]-hexyl}-formamide

Example 22

N-{2R-[4-(4-Acetyl-phenyl)-piperazine-1-carbonyl]-hexyl}-N-hydroxy-formamide

Example 23

N-[2R-(4-Benzhydryl-piperazine-1-carbonyl)-hexyl]-N-hydroxy-formamide

Example 24

N-Hydroxy-N-[2R-(4-phenyl-piperidine-1-carbonyl)-hexyl]-formamide

Example 25

N-Hydroxy-N-{2R-[4-(hydroxy-diphenyl-methyl)-piperidine-1-carbonyl]-hexyl}-formamide

Example 26

N-Hydroxy-N-[2R-(4-phenyl-piperazine-1-carbonyl)-hexyl]-formamide

Example 27

N-(2R-{4-[(4-Chloro-phenyl)-phenyl-methyl]-piperazine-1-carbonyl}-hexyl)-N-hydroxy-formamide

Example 28

N-{2R-[4-(3-Chloro-phenyl)-piperazine-1-carbonyl]-hexyl}-N-hydroxy-formamide

Example 29

N-Hydroxy-N-(2R-{4-[2-(2-hydroxy-ethoxy)-ethyl]-piperazine-1-carbonyl}-hexyl)-formamide

Example 30

N-Hydroxy-N-{2R-[4-(3-hydroxy-propyl)-piperazine-1-carbonyl]-hexyl}-formamide

Example 31

N-Hydroxy-N-{2R-[2-(2-hydroxy-ethyl)-piperazine-1-carbonyl]-hexyl}-formamide

Example 32

N-{2R-[4-(3,4-Dichloro-phenyl)-piperazine-1-carbonyl]-hexyl}-N-hydroxy-formamide

Example 33

N-Hydroxy-N-{2R-[4-(4-methoxy-phenyl)-piperazine-1-carbonyl]-hexyl}-formamide

Example 34

N-Hydroxy-N-{2R-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazine-1-carbonyl]-hexyl}-formamide

Example 35

N-Hydroxy-N-{2R-[4-(1H-indol-7-yl)-piperazine-1-carbonyl]-hexyl}-formamide

Example 36

N-(2R-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazine-1-carbonyl}-hexyl)-N-hydroxy-formamide

Example 37

N-Hydroxy-N-{2R-[4-(4-nitro-phenyl)-piperazine-1-carbonyl]-hexyl}-formamide

Example 38

N-{2R-[4-(4-Fluoro-phenyl)-piperazine-1-carbonyl]-hexyl}-N-hydroxy-formamide

Example 39

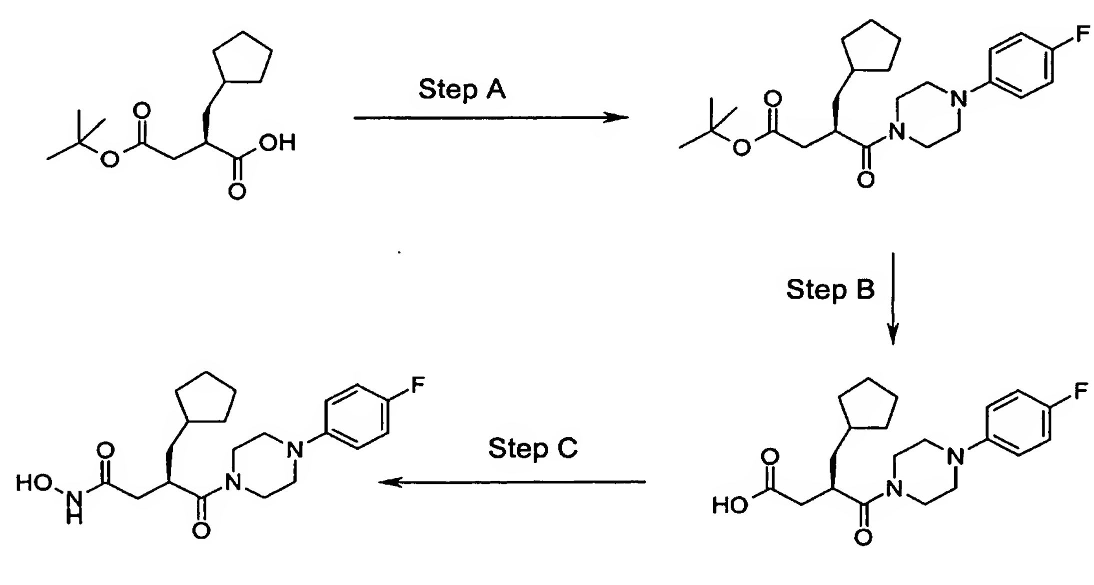
N-{2R-[4-(Furan-2-carbonyl)-piperazine-1-carbonyl]-hexyl}-N-hydroxy-formamide

Example 40

N-{2R-[4-(2,5-Dimethyl-phenyl)-piperazine-1-carbonyl]-hexyl}-N-hydroxy-formamide

The compounds of Examples 41 and 42 below were prepared in solution by parallel synthesis. The general synthetic route (Scheme B) is outlined in detail below for Example 41. 2R-Cyclopentylmethyl-succinic acid 4-*tert*-butyl ester was prepared by analogy with methods in patent application number WO 92/13831

Scheme B



Reagents and conditions: Step A, Amine, PyBOP, HOAt, DIPEA, CH_2Cl_2;
Step B: TFA, CH_2Cl_2; Step C: NH_2OH, NMM, DMF, PyBOP, HOAt, Et_3N, CH_2Cl_2

Example 41

The preparation of 3R-Cyclopentylmethyl-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-N-hydroxy-4-oxo-butyramide

Step A: 3R-Cyclopentylmethyl-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-4-oxo-butyric acid *tert*-butyl ester

To a solution of 2R-Cyclopentylmethyl-succinic acid 4-*tert*-butyl ester **1** (250 mg, 1.0 mmol) in dichloromethane (5 ml) was added PyBOP (670 mg, 1.3 mmol), HOAt (145 mg, 1.0 mmol), DIPEA (278 μl, 1.7 mmol) and amine (211 mg, 1.2 mmol), the reaction mixture was stirred at room temperature for 24 h. The solvent was removed *in vacuo* to yield an orange oil (800 mg), which was taken up in ethyl acetate (50 ml) and was washed with 1M sodium carbonate (2 x 50 ml), water (1 x 50 ml) and dried over anhydrous magnesium sulphate. The solvent was removed *in vacuo* to yield the title compound as a yellow oil (600 mg), which was purified by preparative HPLC.

Step B: 3R-Cyclopentylmethyl-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-4-oxo-butyric acid

To a solution of 3R-Cyclopentylmethyl-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-4-oxo-butyric acid *tert*-butyl ester in dichloromethane (3 ml) was added TFA (2 ml) at 0°C, the reaction mixture was stirred at 0°C for 0.5 h and at room temperature for 1.5 h, after which time no starting material remained. The solvent was removed *in vacuo* and the TFA was azeotroped with toluene to yield the title compound as an orange oil (364 mg), which was progressed to the next step without further purification.

Step C: 3R-Cyclopentylmethyl-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-N-hydroxy-4-oxo-butyramide

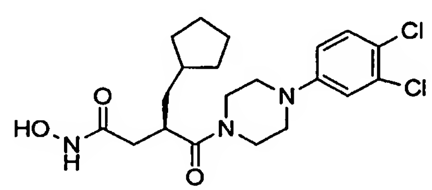
To a solution of 3R-Cyclopentylmethyl-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-4-oxo-butyric acid (364 mg, 1.0 mmol) in dichloromethane (3 ml) was added PyBOP (575 mg,

1.1 mmol), HOAt (14 mg, 0.1 mmol), and Et_3N (279 μl, 2.0 mmol). To a solution of hydroxylamine hydrochloride (105 mg, 1.5 mmol) in a separate flask in DMF (2 ml) was added NMM (161 μl, 1.5 mmol). This solution was then added to the solution of acid and the reaction mixture was stirred at RT for 60 h. The solvent was removed *in vacuo* and the resulting residue was taken up in dichloromethane (5 ml) and was washed with 1M sodium carbonate (1 x 5 ml), water (1 x 5 ml) dried over anhydrous magnesium sulphate and the solvent removed *in vacuo* to yield a yellow oil (520 mg). The product was purified by prep HPLC. LRMS –ve ion: 376 (M-1, 80%), P; +ve ion 345 ([M+1]-32, 40%), P-NHOH; HPLC data: RT 5.6 min 97%

The following compound was prepared in a manner identical to that of Example 41 starting with 2R-Cyclopentylmethyl-succinic acid 4-*tert*-butyl ester and 3,4-dichloro-phenyl-piperazine.

Example 42

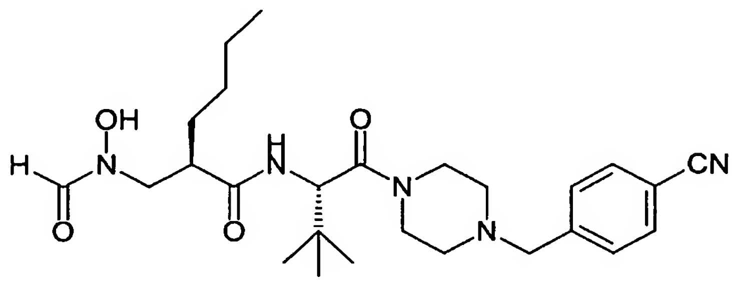
3R-Cyclopentylmethyl-4-[4-(3,4-dichloro-phenyl)-piperazin-1-yl]-N-hydroxy-4-oxo-butyramide



The title compound was purified by preparative HPLC. LRMS –ve ion: 326 (M-1, 40%); +ve ion: 395 ([M+1]-32, 40%), P-NHOH; HPLC data: RT 6.4 min, 98%.

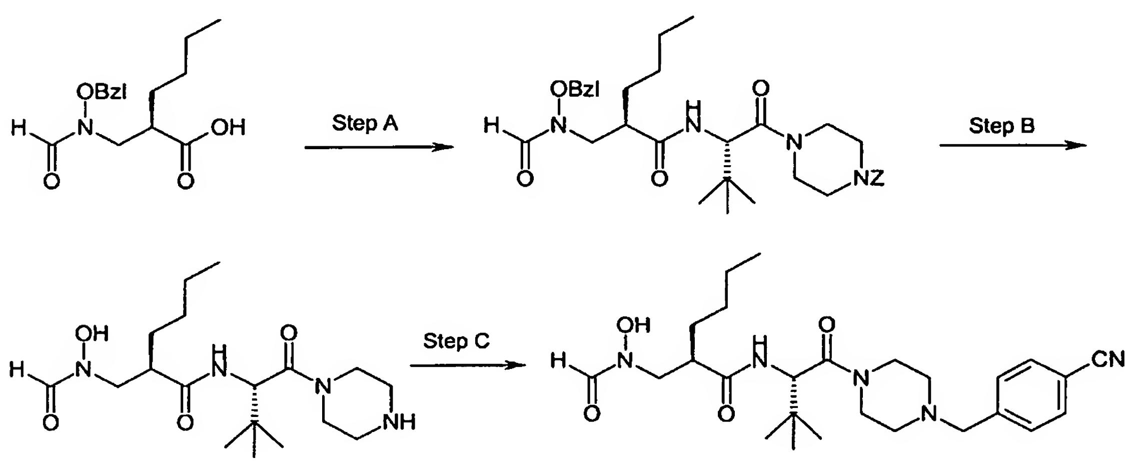
Example 43

2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(4-cyano-benzyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide



The title compound was prepared as detailed below (see Scheme 2) from 2*R*-[(Benzoyloxy-formylamino)-methyl]-hexanoic acid (see Scheme 1).

<u>Scheme 2</u>



Reagents and conditions: A. EDC, HOAt, DMF, amine. B. Pd/C, EtOH, H_2(g). C.Et_3N, DCM, *p*-nitrile benzyl bromide.

Step A: 2*R*-[(Benzyloxy-formyl-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(2-phenoxy-acetyl)-piperazine-1-carbonyl]-propyl}-amide

To a solution of 2R-[(Benzoyloxy-formylamino)-methyl]-hexanoic acid (7.0g, 25 mmols) in DMF was added EDC (5.3 g, 27.5 mmol), 4-(2S-Amino-3,3-dimethyl-butyryl)-piperazine-1-carboxylic acid benzyl ester (10.0 g, 30 mmol) and HOAt (0.34g, 2.5 mmol). The reaction was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate, washed successively with 1M hydrochloric acid, 1M sodium carbonate and saturated sodium chloride solution, dried over anhydrous magnesium sulfate and filtered. The solvent was removed *in vacuo* to yield a yellow oil (9.6 g) that was purified by flash chromatography (3% methanol/DCM) to yield a white foam (6.7g, 45%). ^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.13 (0.6H, s), 7.89 (0.4H, s), 7.36 (10H, m), 6.26 (1H, d, J = 9.2 Hz), 5.15 (2H, s), 4.88 (2H, m), 4.82 (1H, d, J = 9.3 Hz), 3.56 (10H, m), 2.54 (1H, m), 1.25 (6H, m), 0.94 (9H, s), 0.83 (3H, t, J = 6.9 Hz). LRMS: +ve ion 617 [M+Na].

Step B: 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2,2-dimethyl-1*S*-(piperazine-1-carbonyl)-propyl]-amide

To a solution of 2*R*-[(Benzyloxy-formyl-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(2-phenoxy-acetyl)-piperazine-1-carbonyl]-propyl}-amide (6.5 g, 11 mmol) in ethanol (100 ml), under a blanket of argon, was added a suspension of 10% palladium on charcoal (670 mg) in ethyl acetate (15 ml). Hydrogen was bubbled through the suspension for 30 minutes and then the reaction was stirred under an atmosphere of hydrogen for 3 hours 45 minutes. The palladium catalyst was filtered off and the solvent removed *in vacuo* to yield a white foam (4.28 g. 100%). ^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.39 (0.3H, s), 7.80 (0.7H, s), 6.82 (1H, m), 4.90 (1H, m), 3.87 (3H, m), 3.50 (3H, m), 2.80 (5H, m), 1.39 (6H, m), 0.99 (3H, s), 0.95 (6H, s), 0.87 (3H, t, J = 6.7 Hz). LRMS +ve ion 397 [M+1], 419 [M+Na], -ve ion 395 [M-1].

Step C: 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(4-cyano-benzyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

To a stirred solution of 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2,2-dimethyl-1*S*-(piperazine-1-carbonyl)-propyl]-amide in dichloromethane (4 ml) was added triethylamine (85 µl, 0.6 mmol) and *p*-nitrile benzyl bromide (110 mg, 0.56 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* to yield a yellow oil that was purified by preparative HPLC to obtain a white foam (108 mg, 44%) Characterisation data is provided in Table 2.

The compounds of Examples 44-48 were prepared by the synthetic route outlined in Scheme 2 and as described in detail for Example 43. Step C was carried out in parallel for all examples. Characterisation data for the compounds is provided in Table 2. Examples 49-54 were prepared from 2*R*-[(Benzyloxy-formyl-amino)-methyl]-3-cyclopentyl-propionic acid in a similar manner. Characterisation data for the compounds is provided in Table 3. L-*tert*-leucine derivatives were prepared according to established literature methods. Purification of the final compounds, where necessary, was carried out by preparative HPLC.

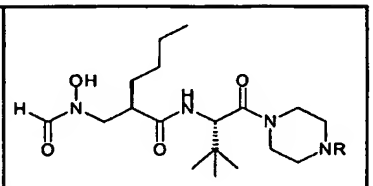
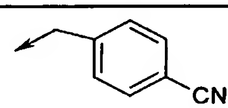
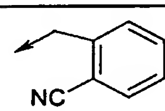
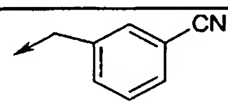
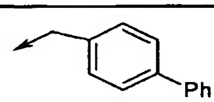
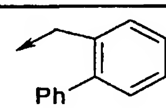
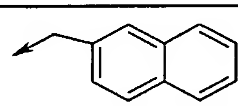
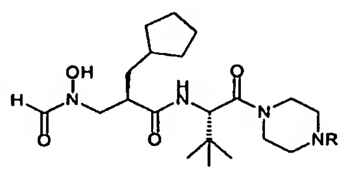
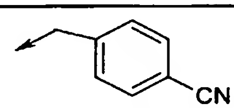
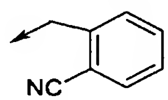
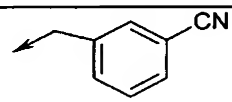
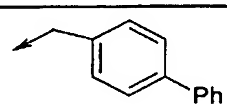
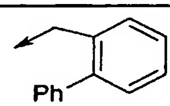
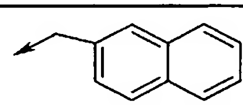
Table 2				
Example	R =	LCMS ions seen	LCMS Retention time (min)	LCMS Purity (%)
43		M+1=486 M+Na=508	2.6	>90
44		M+1=486 M+Na=508	2.65	>90
45		M+1=486 M+Na=508	2.6	>90
46		M+1=537 M+Na=559	3.65	>90
47		M+1=537 M+Na=559	3.58	>90
48		M+1=511 M+Na=533	3.38	>90

Table 3				
Example	R =	LCMS ions seen	LCMS Retention time (mins)	LCMS Purity (%)
49		M+1=512 M+Na=534	2.97	>90
50		M+1=512 M+Na=534	3.02	>90
51		M+1=512 M+Na=534	2.95	>90
52		M+1=563	3.88	>90
53		M+1=563 M+Na=585	3.83	>90
54		M+1=537 M+Na=559	3.63	>90

The compounds of examples 44-54 are named as follows:

Example 44. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(2-cyano-benzyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 45. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(3-cyano-benzyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 46. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [1*S*-(4-biphenyl-4-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-amide

Example 47. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [1*S*-(4-biphenyl-2-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-amide

Example 48. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2,2-dimethyl-1*S*-(4-naphthalen-2-ylmethyl-piperazine-1-carbonyl)-propyl]-amide

Example 49. N-{1*S*-[4-(4-Cyano-benzyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-2*R*-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide

Example 50. N-{1*S*-[4-(2-Cyano-benzyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-2*R*-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide

Example 51. N-{1*S*-[4-(3-Cyano-benzyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-2*S*-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide

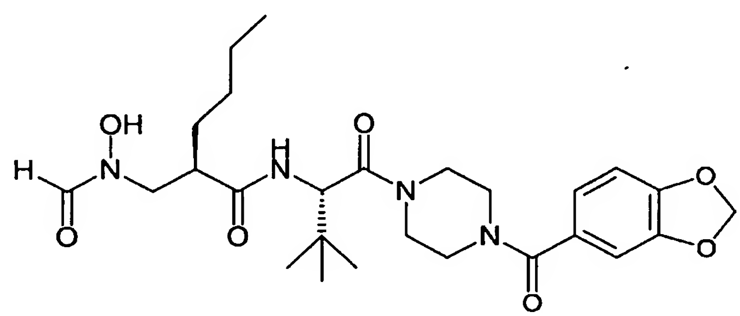
Example 52. N-[1*S*-(4-Biphenyl-4-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-2*R*-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide

Example 53. N-[1*S*-(4-Biphenyl-2-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-2*R*-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide

Example 54. 2*R*-Cyclopentylmethyl-N-[2,2-dimethyl-1*S*-(4-naphthalen-2-ylmethyl-piperazine-1-carbonyl)-propyl]-3-(formyl-hydroxy-amino)-propionamide

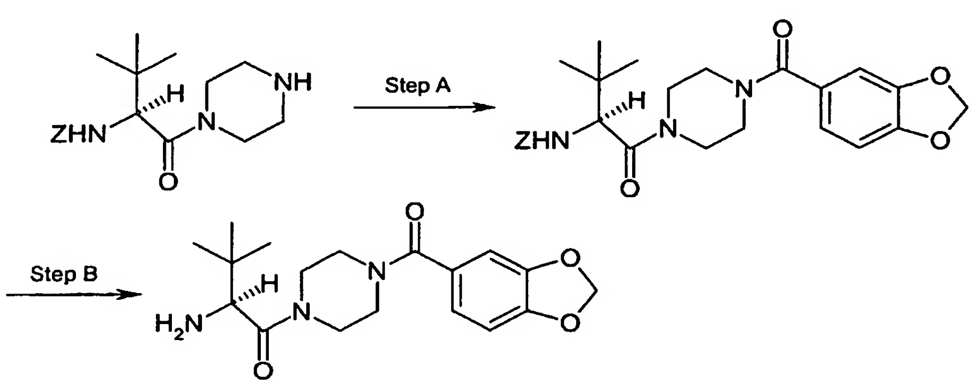
Example 55

2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(3a,7a-dihydro-benzo[1,3]dioxole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide



Example 55 was prepared from 2*R*-[(Benzoyloxy-formylamino)-methyl]-hexanoic acid by analogy with methods described in Scheme 1. 2-Amino-1*S*-[4-(3a,7a-dihydro-benzo[1,3]dioxole-5-carbonyl)-piperazin-1-yl]-3,3-dimethyl-butan-1-one was prepared as detailed below (Scheme 3).

Scheme 3



Reagents and conditions: A. Et_3N, 3,4 methylenedioxybenzoyl chloride, CH_2Cl_2

B. Pd/C, EtOH, H_2(g).

Step A: {1*S*-[4-(3a,7a-Dihydro-benzo[1,3]dioxole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid benzyl ester

To a solution of [2,2-Dimethyl-1*S*-(piperazine-1-carbonyl)-propyl]-carbamic acid benzyl ester (3.2 g, 9.6 mmol) in anhydrous dichloromethane (50 ml) under an atmosphere of argon, was added triethylamine (2.8 ml, 20 mmol) and 3,4 methylenedioxybenzoyl chloride (2.0 g, 10.8 mmol). The reaction was stirred overnight at room temperature. The reaction mixture was diluted with dichloromethane, washed successively with 1M hydrochloric acid, 1M sodium carbonate and saturated sodium chloride solution, dried over anhydrous magnesium sulfate and filtered. The solvent was removed *in vacuo* to yield a yellow oil which was purified by flash chromatography (5% methanol/ dichloromethane) to obtain a white foam (3.5 g, 76%). LRMS: +ve ion 504 [M+Na], ^{1}H-NMR; δ ($CDCl_3$), 7.35 (5H, s), 6.93 (2H, m), 6.84 (1H, m), 6.01 (2H, s), 5.55 (1H, d, J = 9.5 Hz), 5.06 (2H, m), 4.54 (1H, d, J = 9.7 Hz), 3.65 (8H, m), 0.99 (9H, s).

Step B: 2-Amino-1*S*-[4-(3a,7a-dihydro-benzo[1,3]dioxole-5-carbonyl)-piperazin-1-yl]-3,3-dimethyl-butan-1-one

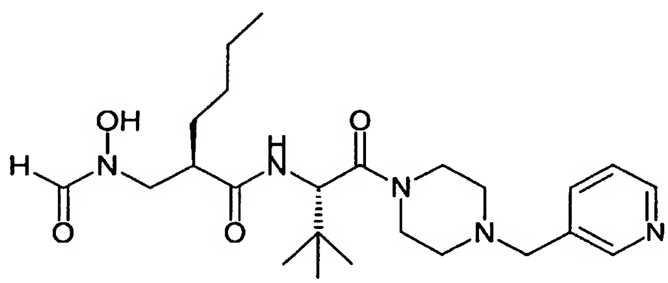
To a solution of {1*S*-[4-(3a,7a-Dihydro-benzo[1,3]dioxole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid benzyl ester (3.5 g, 7.3 mmol) in ethanol (70 ml), under a blanket of argon, was added 10% palladium on charcoal (350 mg). Hydrogen was bubbled through the suspension for 1 hour and then the reaction was stirred under an atmosphere of hydrogen for 2 hours. The palladium catalyst was filtered off and the solvent removed *in vacuo* to yield a white foam (2.5 g. 99%). LRMS: +ve ion 348 [M+1], 370 [M+Na], ^{1}H-NMR; δ ($CDCl_3$), 6.94 (2H, m), 6.84 (1H, m), 6.01 (2H, s), 3.64 (9H, m), 1.61 (2H, s), 0.98 (9H, s).

The following example 56 was prepared in a similar way to Example 55 except 3,4

methylenedioxybenzoyl chloride was replaced with 3-(bromomethyl) pyridine.

Example 56

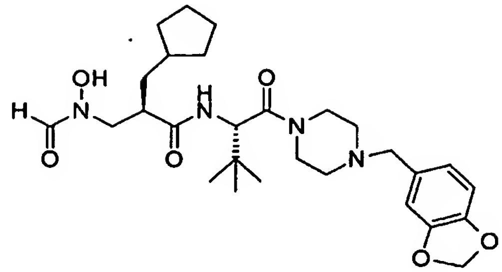
2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2,2-dimethyl-1*S*-(4-pyridin-3-ylmethyl-piperazine-1-carbonyl)-propyl]-amide



[1]H-NMR; δ ($CDCl_3$, rotamers), 8.62 (2H, m), 8.39 (0.4H, s), 7.82 (0.6H, s), 7.67 (1H, d, J=7.7Hz), 7.28 (1H, m), 6.92 (0.4H, m), 6.76 (0.6H, m), 4.91 (1H, m), 4.02 (0.4H, m), 3.82 (3H, m), 3.51 (4.6H, m), 2.84 (0.6H, m), 2.68 (0.4H, m), 2.36 (4H, m), 1.53 (2H, m), 1.25 (4H, m), 0.97 (3H, s), 0.93 (6H, s), 0.88 (3H, t, J = 7.0 Hz). [13]C-NMR; δ (CDCl3), 175.5, 173.3, 170.3, 170.2, 150.6, 149.1, 147.2, 133.6, 123.9, 66.2, 60.3, 54.8, 54.5, 53.7, 53.5, 53.4, 53.3, 53.1, 52.9, 52.8, 52.5, 48.9, 47.3, 47.1, 46.1, 45.1, 2.5 and 42.4. LRMS: +ve ion 484 [M+Na].

Example 57

N-[1*S*-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-2*R*-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide



The title compound was prepared as detailed in scheme 1 from 2*S*-Amino-1-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-3,3-dimethyl-butan-1-one (see scheme 3, piperonyl piperazine is commerically available) and 2*R*-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionic acid pentafluorophenyl ester.

^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.40 (0.4H, bs), 7.82 (0.6H, bs), 6.83 (1H, bs), 6.76-6.63 (2H, m), 6.58-6.54 (1H, m), 5.94 (2H, s), 4.87 (1H, m), 4.10-3.28 (9H, m), 2.87-2.16 (7H, m), 1.85-1.33 (10H, m); 1.09 (1H, m); 0.98 (3.6H, m); 0.93 (5.4H, m); LRMS: +ve ion 531 [M+H], 553 [M+Na]. -ve ion 529 [M-1]; HPLC: RT=4.91 min, 97% pure.

Examples 58-67 were prepared by synthetic methods analogous to those described for Example 55, using the relevant acid chloride or carboxylic acid in Step A of Scheme 3. The compounds were synthesised in parallel and purification of the final compounds, where necessary, was carried out by preparative HPLC. Characterisation data for these compounds are provided in Table 4.

Examples 68-79 were prepared by synthetic methods analogous to those described for Example 43, but using an acid chloride, carboxylic acid or sulfonyl chloride in place of the bromide in Step C of Scheme 2. Purification of the final compounds, where necessary, was carried out by preparative HPLC. Characterisation data for these compounds are provided in Table 5.

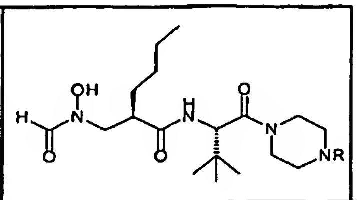
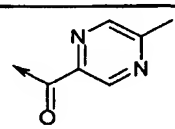
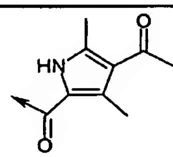
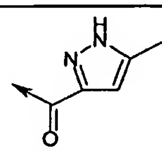
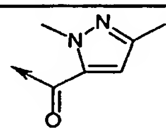
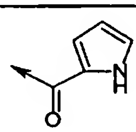
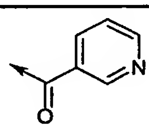
Table 4				
Example	R =	Mass Spec.	HPLC Retention time	HPLC Purity (%)
58		M+Na=513	4.9	>84
59		M+Na=556	5.1	>87
60		M+Na=501	4.8	>84
61		M+Na=515	5	>85
62		M+Na=486	5.1	>83
63		M+Na=498	3.8	>95

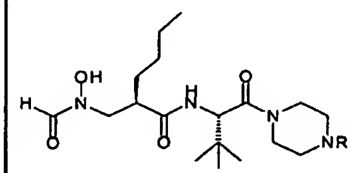
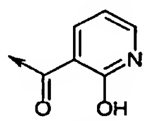
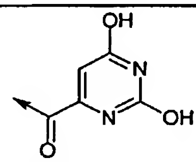
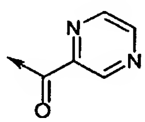
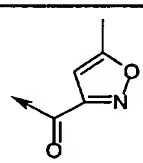
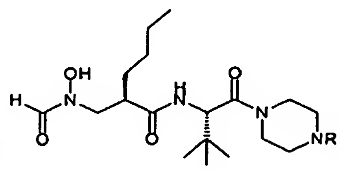
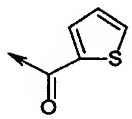
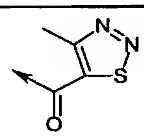
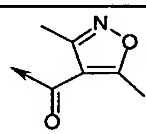
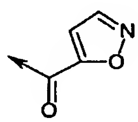
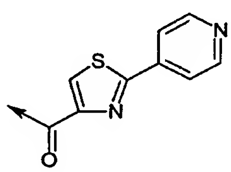
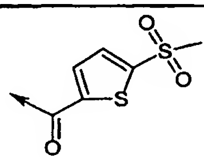
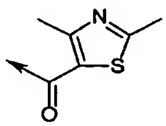
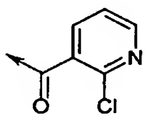
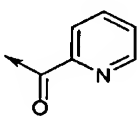
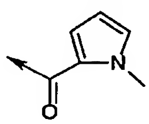
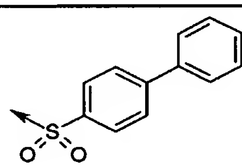
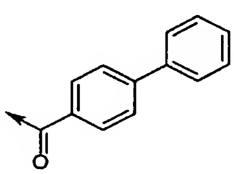
Table 4				
Example	R =	Mass Spec.	HPLC Retention time	HPLC Purity (%)
64		M+Na=514	4.4	98
65		M+Na=531	4.5	93
66		M+Na=499	7.8	>96
67		M+Na=502 M-1=478	10.4	92

Table 5				
Example	R =	Mass Spec.	HPLC Retention time	HPLC Purity (%)
68		M+Na=503 M-1=479	4.9	100
69		M+Na=519 M-1=495	4.9	100
70		M+Na=516 M-1=492	4.7	96
71		M+Na=488 M-1=464	4.6	99
72		M+1=559 M+Na=581 M-1=557	4.5	>88

Example	R =	Mass Spec.	HPLC Retention time	HPLC Purity (%)
73		M+1=559 M+Na=581 M-1=557	5.2	100
74		M+1=510 M+Na=532 M-1=508	5	>95
75		M+Na=532	4.96	99
76		M+1=476 M+Na=498 M-1=474	4.77	95
77		M+1=478 M+Na=500 M-1=476	5.09	100
78		M+1=587 M+Na=609 M-1=585	6.08	100
79		M+1=551 M+Na=573 M-1=549	6.01	97

The compounds of Examples 58 - 79 are named as follows:

Example 58. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(5-methyl-pyrazine-2-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 59. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(4-acetyl-3,5-dimethyl-H-pyrrole-2-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 60. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(5-methyl-1H-pyrazole-3-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 61. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(2,5-dimethyl-2-H-pyrazole-3-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 62. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(1-H-pyrrole-2-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 63. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(pyridine-3-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 64. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(2-hydroxy-pyridine-3-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 65. 2*R*[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(2,6-dihydroxy-pyrimidine-4-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 66. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(pyrazine-2-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 67. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(5-methyl-isoxazole-3-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 68. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(thiophene-2-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 69. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(4-methyl-[1,2,3]thiadiazole-5-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 70. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(3,5-dimethyl-isoxazole-4-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 71. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(isoxazole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 72. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(2-pyridin-4-yl-thiazole-4-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 73. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(5-methanesulfonyl-thiophene-2-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 74. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(2,4-dimethyl-thiazole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 75. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(2-chloro-pyridine-3-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 76. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(pyridine-2-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 77. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(1-methyl-1-H-pyrrole-2-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

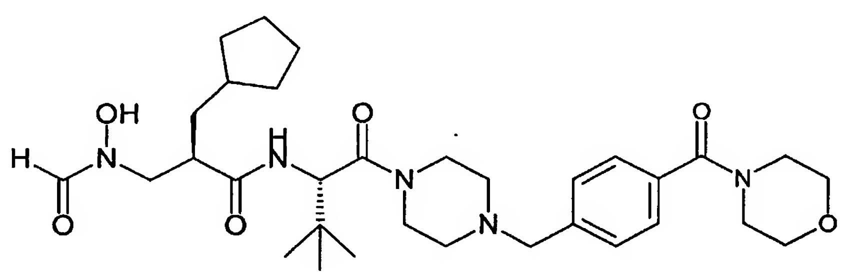
Example 78. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(biphenyl-4-sulfonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 79. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(biphenyl-4-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Examples 80 and 81 were prepared in a similar manner to Example 43 from 2R-[(Benzyloxy-formyl-amino)-methyl]-3-cyclopentyl-propionic acid.

Example 80

2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid (2,2-dimethyl-1*S*-{4-[4-(morpholine-4-carbonyl)-benzyl]-piperazine-1-carbonyl}-propyl)-amide

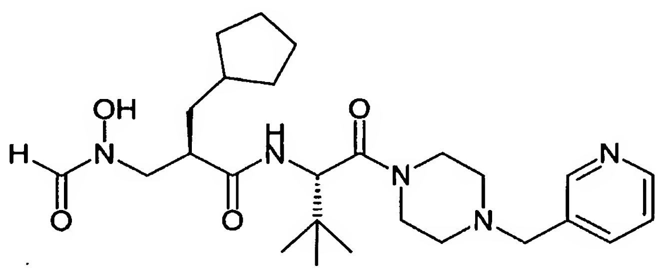


^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.38 (0.4 H, s), 7.81 (0.6H, s), 7.36 (4H, s), 6.77 (0.4H, d, J=8.9Hz), 6.62 (0.6H, d, J=9.3Hz), 4.88 (1H, m), 4.03 (0.4H, dd, J=14.6, 7.1Hz), 3.91 (1H, m), 3.76 (8H, m), 3.51 (5.6H, m), 3.38 (1H, m), 2.84 (0.6H, m), 2.69 (0.4H, m), 2.55 (2H, m), 2.30 (2H, m), 1.57 (9H, m), 1.05 (2H, m), 0.98 (3H, s), 0.94 (6H, s). ^{13}C-NMR; δ ($CDCl_3$, rotamers), 176.0, 173.3, 170.7, 170.1, 156.5,

140.2, 134.8, 129.5, 127.7, 67.3, 62.8, 55.0, 54.5, 53.8, 53.6, 53.2, 53.1, 52.2, 49.0, 47.4, 47.2, 46.0, 44.9, 42.7, 42.4, 38.5, 38.2, 36.9, 36.7, 35.9, 33.2, 27.0, 25.6 and 25.5. LRMS: +ve ion 600 [M+H], 622 [M+Na]. HPLC: RT=4.63 min, 100% pure.

Example 81

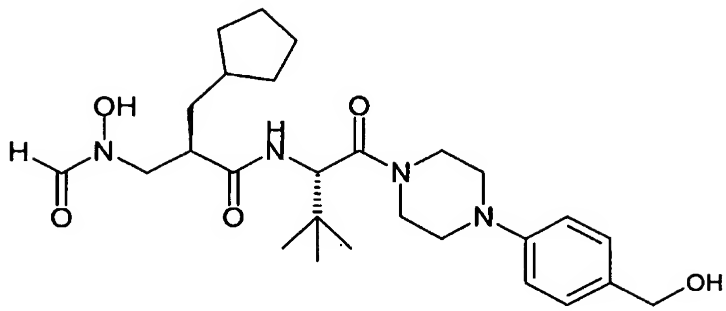
2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2,2-dimethyl-1*S*-(4-pyridin-3-ylmethyl-piperazine-1-carbonyl)-propyl]-amide



[1]H-NMR; δ ($CDCl_3$, rotamers), 8.53 (2 H, m), 8.40 (0.3H, s), 7.81 (0.7H, s), 7.65 (1H, d, J=7.7Hz), 7.27 (1H, m), 6.76 (0.3H, d, J=8.8Hz), 6.67 (0.7H, d, J=8.9Hz), 4.89 (1H, m), 4.03 (0.3H, m), 3.92 (1H, m0, 3.77 (1.7H, m) 3.47 (5H, m), 2.86 (0.7H, m), 2.69 (0.3H, m), 2.56 (2H, m0, 2.31 (2H, m), 1.64 (9H, m), 1.07 (2H, m), 0.98 (3H, s), 0.93 (6H, s). [13]C-NMR; δ ($CDCl_3$, rotamers), 175.5, 173.0, 169.8, 150.3, 148.8, 136.7, 133.1, 123.4, 60.0, 54.6, 54.1, 53.4, 53.2, 52.8, 52.7, 52.1, 48.7, 46.9, 46.8, 45.6, 44.5, 42.2, 42.0, 38.2, 37.9, 36.5, 36.3, 5.6, 32.8, 32.7, 6.7, 25.3 and 25.2. LRMS: +ve ion 488 [M+H], 510 [M+Na]. HPLC: RT=4.48 min, 98% pure.

Example 82

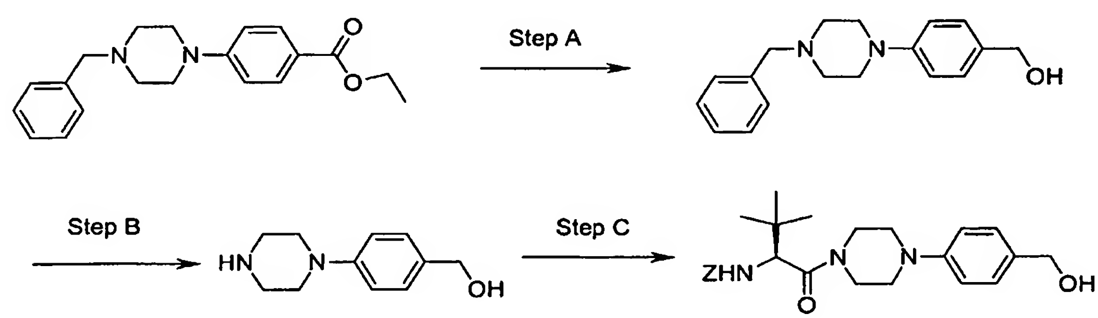
2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(4-hydroxymethyl-phenyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide



LRMS: +ve ion 485 [M-OH]$^+$, -ve ion 501 [M-H]. HPLC RT=5.8 min, 95% pure.

The title compound was prepared from 3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionic acid pentafluoro-phenyl ester and 4-(4-Benzyl-piperazin-1-yl)-benzoic acid ethyl ester which is a known literature compound. {1-[4-(4-Hydroxymethyl-phenyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid benzyl ester (Scheme 4) was deprotected and coupled to the pentafluorophenyl ester in a manner identical to that in Scheme 1.

Scheme 4



Reagents and conditions: A. $LiAlH_4$, THF, 75°C; B. Pd/C, EtOH, H_2 (g); C. EDC, HOAt, Et_3N, CH_2Cl_2.

Step A [4-(4-Benzyl-piperazin-1-yl)-phenyl]-methanol

To a solution of lithium aluminium hydride (88 mg, 2.3 mmol) in dry THF (20 ml) was

added 4-(4-Benzyl-piperazin-1-yl)-benzoic acid ethyl ester (500 mg, 1.5 mmol). The suspension was stirred at 75 °C for 4 h. The reaction mixture was allowed to cool and a few drops of water were added followed by 1-2 drops of 1M sodium hydroxide. A white precipitate formed and was filtered off, the THF was removed *in vacuo*, and brine (10 ml) was added to the residue. This mixture was washed with ether (2 x 50 ml, the ether layers were combined and dried over anhydrous magnesium sulphate and the solvent removed *in vacuo* to yield a yellow solid (405 mg). Flash chromatography (3%MeOH/CH_2Cl_2) allowed the isolation of the title compound as a white solid (331 mg, 76%). ^{1}H-NMR δ ($CDCl_3$) 7.38-7.21 (7H, m, ArH), 6.91-6.85 (2H, m, ArH), 4.59 (2H, s), 3.57 (2H, s), 3.21-3.17 (4H, m), 2.61-2.58 (4H, m). HPLC: 2.4 min (99% @ 214 nm); LRMS +ve: 283 (M+1, 80).

Step B: (4-Piperazin-1-yl-phenyl)-methanol

To a solution of [4-(4-Benzyl-piperazin-1-yl)-phenyl]-methanol in EtOH (50 ml) under a blanket of argon was added a suspension of 10% palladium on charcoal (1.5 g) in EtOH (150 ml). Hydrogen was bubbled through the suspension for 1 h and then the reaction mixture was stirred under a blanket of hydrogen for 60 h at RT. The catalyst was filtered off and the solvent removed *in vacuo* to yield the title compound as a white solid (4.8 g, 100%). ^{1}H-NMR δ ($CDCl_3$) 7.30-7.21 (2H, m, ArH), 6.94-6.88 (2H, m, ArH), 4.59 (2H, s), 3.18-2.98 (8H, m). HPLC: 0.5 min (37% @ 214 nm), 0.7 min (55% @ 214 nm), multiple peaks due to salt formation from TFA buffer; LRMS +ve: 193 (M+1, 70).

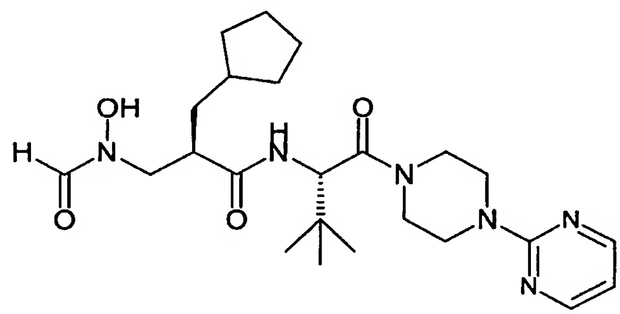
Step C: {1-[4-(4-Hydroxymethyl-phenyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid benzyl ester

To a solution of CBz protected *tert*-leucine (7.4 g, 28 mmol) in dichloromethane (20 ml) was added (4-Piperazin-1-yl-phenyl)-methanol in a solution of DMF/ dichloromethane (50:50, 250 ml). EDC (7.3 g, 38 mmol), HOAt (0.34g, 2.5 mmol) and triethylamine (7.0 ml, 50 mmol) were subsequently added. The reaction mixture

was stirred at RT for 18 h. The solvent was removed *in vacuo* to yield a yellow oil, which was taken up in dichloromethane (300 ml) and was washed with 1M sodium carbonate (2 x 200 ml), 1M hydrochloric acid (1 x 200 ml), brine (1 x 200ml) dried (anhydrous magnesium sulphate) and the solvent removed *in vacuo* to yield a white foam (11.8 g). Flash chromatography 2% MeOH/dichloromethane allowed the isolation of the title compound as a white foam (7.01 g, 63%). HPLC 5.7 min (100% @ 214 nm). LRMS +ve 462 (M+Na, 60), 440 (M+1, 20), 422 (M-OH, 100).

Example 83

2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2,2-dimethyl-1*S*-(4-pyrimidin-2-yl-piperazine-1-carbonyl)-propyl]-amide

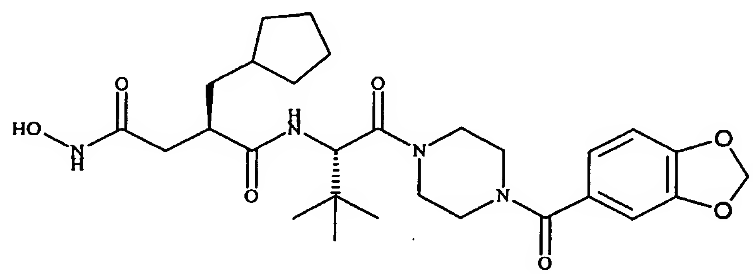


Prepared by method analogous to Example 82.

^{1}H-NMR; δ ($CDCl_3$), 8.40 (0.3H, s), 8.33 (2H, d, J=4.8Hz), 7.82 (0.7H, s), 6.76 (1H, d, J=8.4Hz), 6.55 (1H, t, J=4.7Hz), 4.94 (1H, m), 4.09-3.37 (10H, m), 2.86-2.78 (0.7H, m), 2.72-2.65 (0.3H, m,) 1.63-1.18 (6H, m), 1.02 (3H, s), 0.97 (6H, s), 0.85 (3H, m). ^{13}C-NMR; δ ($CDCl_3$), 176.0, 173.3, 170.5, 161.9, 158.2, 111.1, 55.3, 54.7, 52.1, 48.7, 47.1, 47.0, 46.5, 45.1, 44.3, 44.2, 44.0, 43.9, 42.6, 42.4, 35.9, 30.3, 30.2, 29.7, 29.6, 27.1, 22.9 and 14.3. LRMS: +ve ion 449 [M+H], 471 [M+Na], -ve ion 447 [M-H]. HPLC: RT=4.99 min, 100% pure.

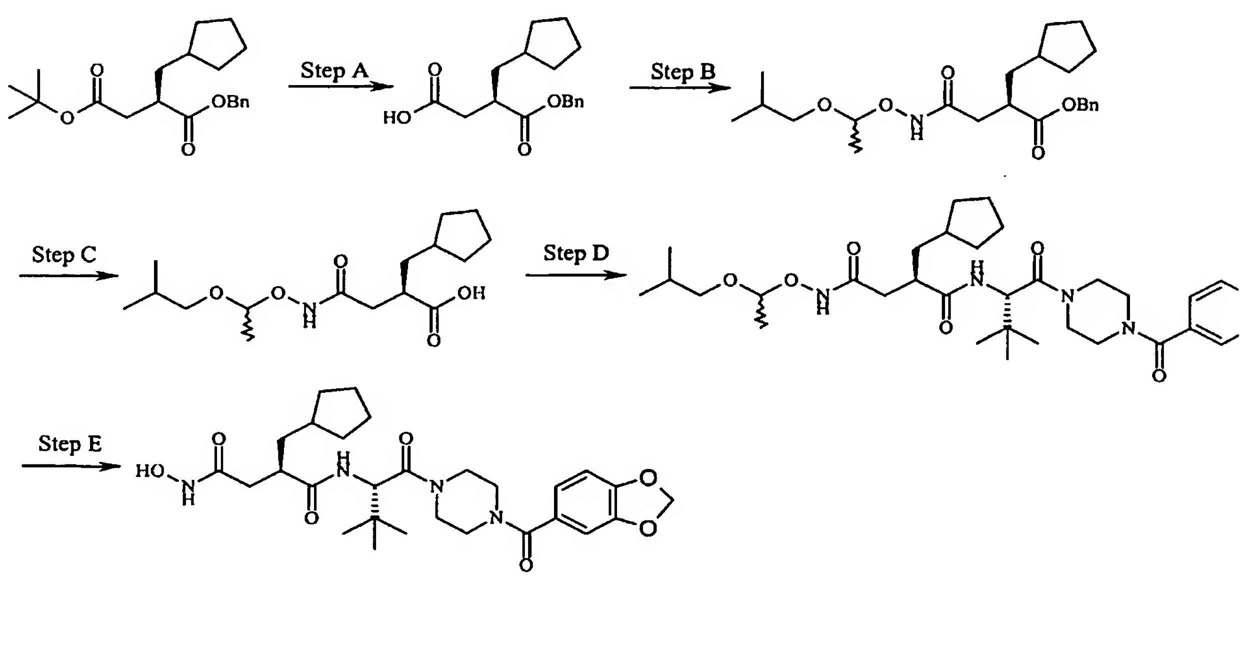
Example 84

N^1-{1*S*-[4-(Benzo[1,3]dioxole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-2*R*-cyclopentylmethyl-N^4-hydroxy-succinamide



Example 84 was prepared as detailed below (see Scheme 5) from 2*R*-Cyclopentylmethyl-succinic acid 4-*tert*-butyl ester, prepared by analogous methods described in patent WO 92/13831, and 2-Amino-1*S*-[4-(benzo[1,3]dioxole-5-carbonyl)-piperazin-1-yl]-3,3-dimethyl-butan-1-one, prepared by methods described in Scheme 3.

Scheme 5



Reagents and conditions: A. TFA, CH_2Cl_2; B. EDC, DMF, HOAt, hydroxylamine. C. Pd/C, EtOH, $H_{2\,(g)}$. D. EDC, DMF. E. MeOH, 1M HCl.

Step A: 2*R*-Cyclopentylmethyl-succinic acid 1-benzyl ester

To a solution of 2*R*-Cyclopentylmethyl-succinic acid 4-*tert*-butyl ester (960 mg, 2.7 mmol) in dichloromethane (30 ml), was added TFA (30 ml). The reaction mixture was left at –4 °C for 18h. The solvent was removed *in vacuo* and the TFA co-evaporated with toluene and ether *in vacuo* to yield a yellow oil (810 mg, 100%).
^{1}H-NMR δ ($CDCl_3$), 7.38-7.29 (5H, m), 5.15 (2H, s), 2.93-2.87 (1H, m), 2.78 (1H, dd, J_1=9.485 J_2=16.81), 2.52 (1H, dd, J_1=4.92 J_2=17.01), 1.84-1.63 (3H, m), 1.62-1.53 (2H, m), 1.52-1.40 (3H, m), 1.09-1.02 (2H, m).

Step B: 2*R*-Cyclopentylmethyl-*N*-(1-isobutoxy-ethoxy)-succinamic acid benzyl ester

To a solution of 2*R*-Cyclopentylmethyl-succinic acid 1-benzyl ester (810 mg, 2.8 mmol) in DMF, was added EDC (805 mg, 4.2 mmol), HOAt, (10% w/w) and O-(1-Isobutoxy-ethyl)-hydroxylamine (745 mg, 5.6 mmol). The reaction was left stirring for 60 h at room temperature. The solvent was removed *in vacuo*, the residue was taken up in ethyl acetate and washed successively with 1M hydrochloric acid, 1M sodium carbonate and saturated sodium chloride solution. The organic phase was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield a yellow oil (1.07g, 97%).
^{1}H NMR; δ ($CDCl_3$), 8.05 (1H, bs), 7.34-7.27 (5H, m), 5.17:5.10 (2H, AB q, J=12.36), 4.92-4.88 (1H, m), 3.52 (1H, dd, J_1=6.643 J_2=9.340), 3.271 (1H, dd, J_1=6.734 J_2=9.267), 3.06-2.95 (1H, m), 2.52-2.23 (2H, m), 1.89-1.41 (11H, m), 1.36 (3H, dd, J_1=3.53 J_2=5.303), 1.06 (2H, bs), 0.919 (6H, d, 6.63).
ESMS; +ve ion 428 [M+Na]

Step C: 2*R*-Cyclopentylmethyl-*N*-(1-isobutoxy-ethoxy)-succinamic acid

To a solution of 2*R*-Cyclopentylmethyl-*N*-(1-isobutoxy-ethoxy)-succinamic acid benzyl ester (925 mg, 2.3 mmol) in ethanol, under a blanket of argon, was added palladium on charcoal (10% w/w). Hydrogen was bubbled through the suspension for 30 minutes and the reaction stirred under an atmosphere of hydrogen for 3 hours. The palladium catalyst was filtered off and the solvent removed *in vacuo* to yield a yellow oil (720 mg, 100%).

^{1}H-NMR; δ ($CDCl_3$), 4.93 (1H, m), 3.559 (1H, dd, J_1= 6.620 J_2= 9.292), 3.292 (1H, dd, J_1= 6.70 J_2= 9.330), 2.94 (1H, m), 2.49-2.29 (2H, m), 1.93-1.75 (5H, m), 1.61-1.44 (6H, m), 1.377 (3H, dd, J_1= 1.237 J_2= 5.237), 1.08 (2H, m), 0.919 (6H, d, J_1= 6.65).
ESMS; +ve ion 338 [M+Na], -ve ion 314 [M-1]

Step D: *N*^{1}-{1*S*-[4-(Benzo[1,3]dioxole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-2*R*-cyclopentylmethyl-*N*^{4}-(1-isobutoxy-ethoxy)-succinamide

To a solution of 2*R*-Cyclopentylmethyl-*N*-(1-isobutoxy-ethoxy)-succinamic acid (150 mg, 0.48 mmol) in DMF (7.5 ml), was added 2-Amino-1*S*-[4-(benzo[1,3]dioxole-5-carbonyl)-piperazin-1-yl]-3,3-dimethyl-butan-1-one (165 mg, 0.5 mmol) and stirred for 5 minutes. EDC (96 mg, 0.5 mmol) was added and the reaction mixture stirred at room temperature over the weekend. The solvent was removed *in vacuo* and the residue taken up in ethyl acetate and washed successively with 1M hydrochloric acid, 1M sodium carbonate and saturated sodium chloride solution. The organic phase was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield an 'off white' solid (227mg, 74%).

^{1}H-NMR; δ ($CDCl_3$), 6.87 (2H, m), 6.01 (2H, s), 4.873 (1H, m), 3.94-3.67 (4H, m), 3.64-3.23 (10H, m), 2.773 (1H, m), 2.43-2.19 (2H, m), 1.89-1.39 (14H, m), 1.357 (3H, dd, J_1= 2.350 J_2=5.306), 1.117 (2H, m), 0.987 (9H, s), 0.913 (6H, d,

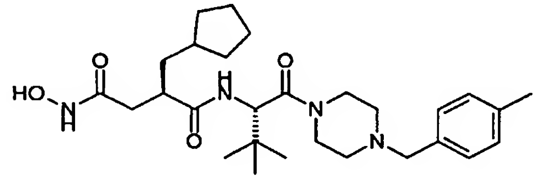
J_1=6.66).ESMS; +ve ion 667 [M+Na]

Step E: *N*[1]-{1*S*-[4-(Benzo[1,3]dioxole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-2*R*-cyclopentylmethyl-*N*[4]-hydroxy-succinamide

N[1]-{1*S*-[4-(Benzo[1,3]dioxole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-2*R*-cyclopentylmethyl-*N*[4]-(1-isobutoxy-ethoxy)-succinamide(198 mg, 0.31 mmol) was dissolved in a 50/50 mixture of methanol and 1M hydrochloric acid (16 ml) and stirred at room temperature for 30 minutes. Pre-washed Amberlyst resin 95 was added until pH 7 was reached and was then filtered under suction and washed with methanol. The filtrate was concentrated *in vacuo* with ethanol to yield a yellowish solid that was purified by preparative HPLC to yield the title compound as a white foam (62 mg). ^{1}H-NMR; δ (MeOD), 6.935 (1H, s), 6.926 (2H, dd, J_1= 7.854 J_2= 34.375), 6.018 (2H, s), 4.863 (1H, s), 3.902-3.384 (8H, m), 2.893 (1H, m), 2.323 (1H, dd, J_1=7.86 J_2=14.31), 2.193 (1H, dd, J_1=6.23 J_2=14.39), 1.824 (1H, m), 1.645 (5H, m), 1.491 (2H, m), 1.374 (1H, m), 1.033 (11H, m); ^{13}C-NMR; δ (MeOD), 177.7, 172.8, 172.2, 171.0, 151.3, 149.7, 130.2, 123.3, 109.7, 103.5, 56.5, 48.1, 43.6, 43.4, 40.1, 39.8, 37.4, 36.4, 34.0, 27.5, 26.5; ESMS; +ve ion 567 [M+Na], -ve ion 543 [M-1]

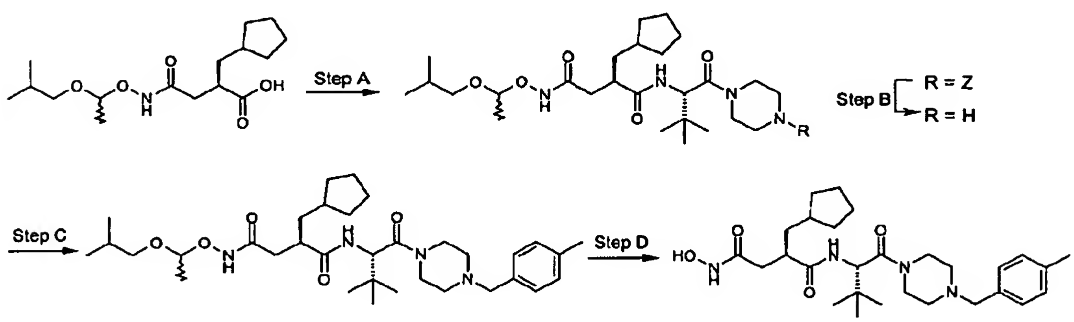
Preparative Example A

2*R*-Cyclopentylmethyl-*N*[1]-{2,2-dimethyl-1*S*-[4-(4-methyl-benzyl)-piperazine-1-carbonyl]-propyl}-*N*[4]-hydroxy-succinamide



The title compound was prepared as detailed below (see scheme 6) from 2-Cyclopentylmethyl-*N*-(1-isobutoxy-ethoxy)-succinamic acid (scheme 5).

Scheme 6



Reagents and conditions: A. 4-(2-Amino-3,3-dimethyl-butyryl)-piperazine-1-carboxylic acid benzyl ester, WSC, NEt_3, CH_2Cl_2; B. Pd/C, H_2, MeOH; C. 4-methyl benzyl bromide, NEt_3, CH_2Cl_2; D. HCl 1N, MeOH.

Step A: 4-{2*S*-[2*R*-Cyclopentylmethyl-3-(1-isobutoxy-ethoxycarbamoyl)-propionylamino]-3,3-dimethyl-butyryl}-piperazine-1-carboxylic acid benzyl ester

To a cold (0°C) solution of the acid (6.8 g, 16.1 mmol) in dichloromethane (80 ml), the hydrochloride salt of the amine (8.65 g, 19.4 mmol) was added followed by triethylamine (2.92 ml, 21 mmol) and then WSC (3.72 g, 19.4 mmol). The reaction mixture was stirred overnight allowing the temperature to come back to room temperature. The reaction mixture was then diluted with dichloromethane and washed with water (80 ml), with Na_2CO_3 and brine. The combined organic layer was dried over $MgSO_4$ and the solvent was removed in *vacuo* to yield a yellowish foam which was purified through flash chromatography to give a 100% pure compound (8 g, 79% yield).

^{1}H-NMR; δ ($CDCl_3$), 8.20 (1H,m), 7.32 (5H, m), 6.45 (1H, m), 5.11 (2H, s), 4.91-4.82 (2H, m), 3.87-3.21 (12H, m), 2.41 (1H, m), 2.73 (1H, m), 1.90-1.40 (14H, m), 1.36 (3H, m), 0.98 (9H, s), 0.90 (6H, d)

Step B: 2*R*-Cyclopentylmethyl-*N*[1]-[2,2-dimethyl-1*S*-(piperazine-1-carbonyl)-propyl]-*N*[4]-(1-isobutoxy-ethoxy)-succinamide

To a suspension of the Z-protected piperazine (8 g, 12.7 mmol) in MeOH (100 ml) was added Pd/C (0.8 g) and then H_2 was bubbled for 1h. The reaction mixture was then stirred under a blanket of H_2 for another hour. Pd/C was filtered off through a celite pad to give the desired compound in a 99% yield.

ESMS; +ve ion 498 [M+1], -ve ion 496 [M-1]; HPLC: RT = 5.21 min

Step C: 2*R*-Cyclopentylmethyl-*N*[1]-{2,2-dimethyl-1*S*-[4-(4-methyl-benzyl)-piperazine-1-carbonyl]-propyl}-*N*[4]-(1-isobutoxy-ethoxy)-succinamide

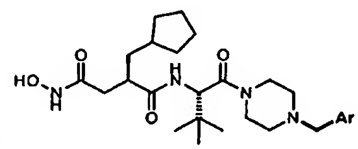
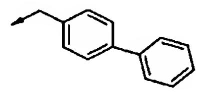
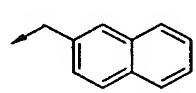
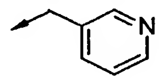
To a solution of 4-methyl benzyl bromide (74 mg, 0.4 mmol) in dichloromethane (2 ml) were added a solution of the piperazine in dichloromethane (1.2 ml, 0.33 mmol) and Net_3 (60 ml, 0.4 mmol). The reaction mixture was stirred at room temperature for 12 hours. Water was added (1.5 ml) and the resulting solution filtered through polypropylene hydrophobic cartridges (1PS filter). The solvent was then removed under reduced pressure to afford the expected adduct.

Step D: 2*R*-Cyclopentylmethyl-*N*[1]-{2,2-dimethyl-1*S*-[4-(4-methyl-benzyl)-piperazine-1-carbonyl]-propyl}-*N*[4]-hydroxy-succinamide

To a solution of the latter in MeOH (4 ml) was added HCl 1N (600 ml) and the reaction mixture was stirred for 2 h. Then 60 ml of NEt_3 were added and the solvent was removed under reduced pressure. The crude reaction mixture was purified through HPLC.

The compounds of Examples 85-87 were prepared by the synthetic route outlined in Scheme 5 and as described in detail for Preparative Example A. Step C and Step D were carried out in parallel format for all examples. Characterisation data for the

compounds are provided in Table 6.

Table 6			
Example	**Structures**	**Mass Spec**	**Retention Time (min)**
85		M+1=563 M-1=561	5.2
86		M+1=537 M-1=535	5.03
87		M+1=488 M-1=486	4.17

The compounds of Examples 85 - 87 are named as follows:

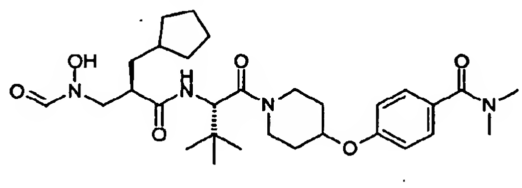
Example 85. *N*[1]-[1*S*-(4-Biphenyl-4-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-2*R*-cyclopentylmethyl-*N*[4]-hydroxy-succinamide

Example 86. 2*R*-Cyclopentylmethyl-*N*[1]-[2,2-dimethyl-1*S*-(4-naphthalen-2-ylmethyl-piperazine-1-carbonyl)-propyl]-*N*[4]-hydroxy-succinamide

Example 87. 2*R*-Cyclopentylmethyl-*N*[1]-[2,2-dimethyl-1*S*-(4-pyridin-3-ylmethyl-piperazine-1-carbonyl)-propyl]-*N*[4]-hydroxy-succinamide

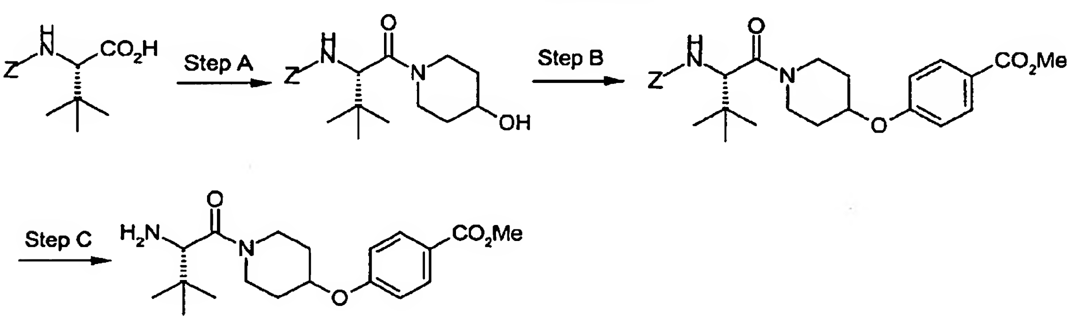
Example 88

4-(1-{2*S*-[3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-N,N-dimethyl benzamide



The title compound was prepared as detailed below (see scheme 8) from the the 3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionic acid pentafluorophenyl ester and 4-[1-(2*S*-Benzyloxycarbonylamino-3,3-dimethyl-butyryl)-piperidin-4-yloxy]-benzoic acid methyl ester (see scheme 7).

Scheme 7



Reagents and conditions: Step A: 4-hydroxy piperidine,WSC, HOAt, CH_2Cl_2; Step B: 4-hydroxy methyl benzoate, DEAD, PPh_3, THF; Step C: H_2, Pd/C, EtOH, reflux

Step A: [1*S*-(4-Hydroxy-piperidine-1-carbonyl)-2,2-dimethyl-propyl]-carbamic acid benzyl ester

To a cold solution (0°C) of the Z-*tert*-leucine (3.48 g, 13.1 mmol) and 4-hydroxy piperidine (1.4 g, 13.7 mmol) in CH_2Cl_2 (40 ml) were added WSC (2.75 g, 14.4 g) followed by HOAt (18 mg, 0.13 mmol). The reaction mixture was stirred at room

temperature for 12 hours and then washed with water and brine. The combined organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to furnish a yellow oil which was purified through flash chromatography. The desired compound was obtained in 64% yield.

^{1}H NMR; δ ($CDCl_3$), 7.34 (5H, s), 5.58 (1H, m), 5.08 (2H, m), 4.60 (1H, m), 3.91 (3H, m), 3.49-3.05 (2H, m), 1.91 (4H, m), 0.98 (9H, d, J=3.57); ESMS; +ve ion 371 [M+Na]; HPLC: RT = 5.44 min.

Step B: 4-[1-(2*S*-Benzyloxycarbonylamino-3,3-dimethyl-butyryl)-piperidin-4-yloxy]-benzoic acid methyl ester

To a cold solution (0°C) of the latter compound (1.45 g, 4.2 mmol), 4-hydroxy methyl benzoate (0.7 g, 4.6 mmol) and triphenylphosphine (1.48 g, 5.46 mmol) were added dropwise followed by the addition of DEAD (0.86 ml, 5.46 mmol). The reaction mixture was stirred at 0°C for 2.5 hours. Thf was removed in *vacuo* and the crude residue was taken-up in ethyl acetate. The organic layer was washed with water and brine and subsequently dried over $MgSO_4$. After purification through flash chromatography the expected compound was obtained as a pure white foam in 70% yield.

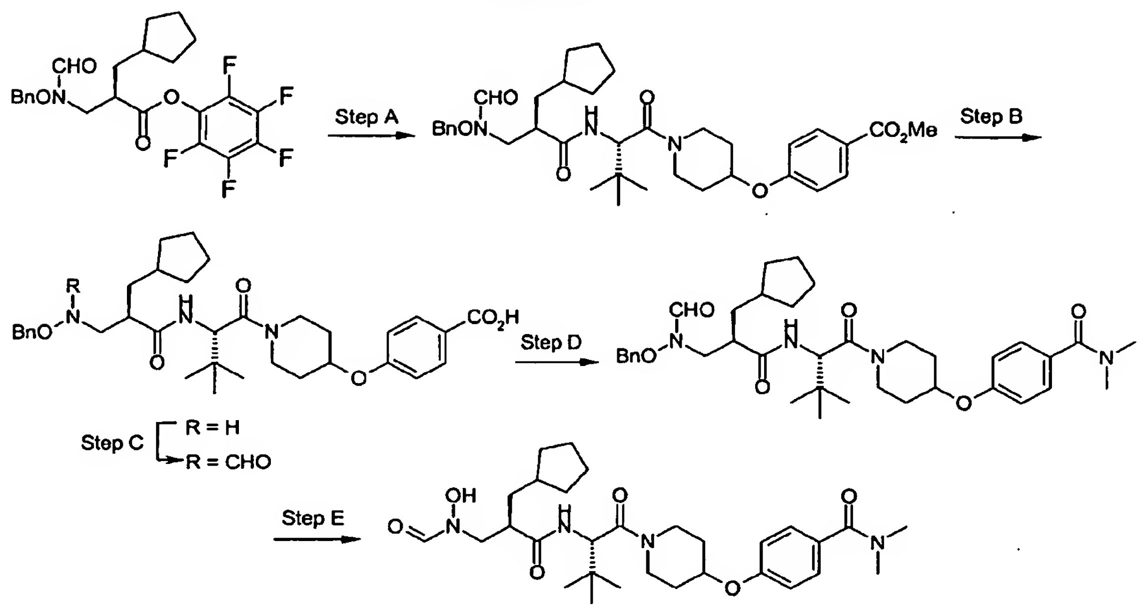
^{1}H NMR; δ ($CDCl_3$), 7.99 (2H, dd, J_1=1.23 J_2=8.82), 7.35 (5H, m), 6.92 (2H, dd, J_1=1.18 J_2=8.76), 5.58 (1H, m), 5.09 (2H, m), 4.62 (2H, m), 3.89 (4H, m), 3.72 (1H, m), 3.61 (2H, m), 1.90 (4H, m), 0.99 (9H, s); ESMS; +ve ion 505 [M+Na]; HPLC: RT = 6.73 min.

Step C: 4-[1*S*-(2-Amino-3,3-dimethyl-butyryl)-piperidin-4-yloxy]-benzoic acid methyl ester

To a solution of the latter compound (650 mg, 1.35 mmol) in EtOH (10 ml) was added Pd/C (65 mg) and H_2 was bubbled through the resulting suspension for 4 hours. Pd/C was then removed by filtration through a celite pad. The solvent was removed under reduced pressure to give the desired compound in quantitative yield.

^{1}H NMR; δ ($CDCl_3$), 7.99 (2H, d, J= 8.82), 6.92 (2H, d, J= 8.47), 4.65 (1H, m), 3.89 (3H, s), 3.72 (2H, m), 3.56 (1H, d, J= 4.82), 1.95 (4H, m), 0.99 (9H, s); ESMS; +ve ion 349 [M+1].

Scheme 8



Reagents and conditions: Step A: RHS, NEt_3, DMF; Step B: LiOH, THF, MeOH, H_2O; Step C: FAA, NEt_3, THF; Step D: dimethyl amine, WSC, HOAt, CH_2Cl_2; Step E: Cyclohexene, Pd/C, EtOH, reflux

Step A: 4-(1-{2*S*-[3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-benzoic acid methyl ester

To a solution of the amine (3.4 g, 9.70 mmol) in DMF were added the PFP ester (4 g, 8.50 mmol) followed by NEt_3 (1.3 ml, 9.34 mmol). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude dissolved in ethyl acetate. The work-up was made by means of water, sodium carbonate, ammonium chloride and brine. The combined organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to yield a foam. The crude product was purified through flash chromatography to yield the desired compound as a white foam in 98% yield.

^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.01-7.96 (2H, m), 7.38 (5H, bs), 6.93-6.88 (2H, m), 6.32-6.29 (1H, m), 5.01-4.52 (7H, m), 4.02-3.52 (7H, m), 3.89 (3H, s), 2.68-2.50 (1H, m), 1.98-1.34 (15H, m), 0.95 (9H, s); LRMS: +ve ion 436 [M+H], 658 [M+Na]. HPLC: RT=6.79 min, 98% pure.

Step B: 4-{1-[2*S*-(3-Benzyloxyamino-2*R*-cyclopentylmethyl-propionylamino)-3,3-dimethyl-butyryl]-piperidin-4-yloxy}-benzoic acid

To a cold solution (0°C) of the latter compound (100 mg, 0.16 mmol) in a mixture of THF/MeOH/H_2O (3:1:1; 2.5 ml) was added LiOH (33 mg). The reaction mixture was stirred for 48 hours at room temperature. The solvent was removed under *vacuo* and the crude dissolved in water. The aqueous layer was extracted by means of Et_2O and then acidified to pH=1 by means of HCl 1N. The desired product was then extracted from Et_2O. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to yield the desired compound as a white solid in 61% yield.

^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.06-8.01 (2H, m), 7.38-7.30 (5H, m), 7.09-6.99 (1H, 2d, J=9.3Hz), 6.94-6.89 (2H, m), 5.02 (1H, d, J=9.4Hz), 4.75 (2H, s), 4.69-4.61 (1H, m), 4.08-3.67 (4H, m), 3.58-3.42 (2H, m), 3.17-3.01 (2H, m), 2.62 (1H, m), 2.10-1.40 (15H, m), 1.01 (9H, s); LRMS: +ve ion 594 [M+H], -ve ion 592 [M-1]. HPLC: RT=5.92 min, 98% pure.

Step C: 4-(1-{2*S*-[3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-benzoic acid

To a cold (0°C) of the acid (4.8 g, 8.1 mmol) in THF (100 ml) were added the mixed anhydride (1.8 g, 20.3 mmol) and NEt_3 (3.33 ml, 24.3 mmol). The reaction mixture was stirred at room temperature for 12 hours. The solvent was then removed under reduced pressure and the residue was dissolved in CH_2Cl_2. The organic layer was washed with wate and brine and dried over $MgSO_4$. The solvent was removed in *vacuo* to yield the desired derivative.

^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.19-7.89 (3H, bs), 7.46-7.30 (5H, m), 7.02-6.85 (1H, m), 5.02-4.53 (4H, m), 4.04-3.37 (6H, m), 2.70 (1H, m), 1.98-1.35 (15H, m), 0.97 (9H, s); LRMS: +ve ion 644 [M+Na], -ve ion 620 [M-1] HPLC: RT=6.29 min, 95% pure.

Step D: 4-(1-{2*S*-[3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-N,N-dimethyl-

benzamide

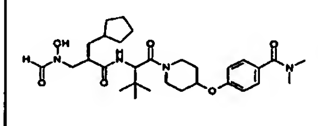
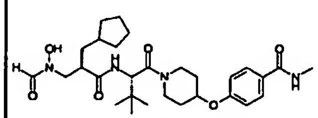
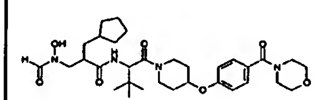
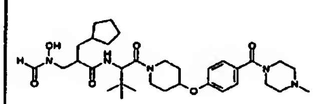
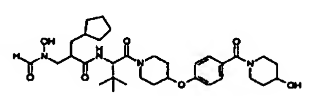
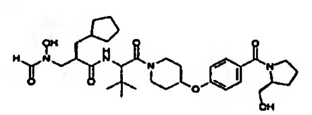
To a cold (0°C)solution of the starting acid (.35 g, 0.56 mmol) in CH_2Cl_2 (8 ml) were added dimethyl amine (0.67 mmol), WSC (118 mg, 0.61 mmol) and HOAt (8 mg, 0.06 mmol). The reaction mixture was stirred at room temperature for 12 hours. Water was added (3 ml) and the resulting solution filtered through polypropylene hydrophobic cartridges (1PS filter). The solvent was then removed under reduced pressure to afford the expected adduct. The crude compound was then purified through flash chromatography to afford a 100% pure compound with a 55% yield.

LRMS: +ve ion 671 [M+Na], HPLC: RT=6.32 min, 100% pure.

Step E: 4-(1*S*-{2-[2*R*-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-*N,N*-dimethyl-benzamide

To a solution of the latter compound (200 mg, 0.31 mmol) were added cyclohexene (0.5 ml) and Pd/C (24 mg). The reaction mixture was stirred to reflux for 3 h. Pd/C was then filtered off through a celite pad. The solvent was removed under reduced pressure to afford the desired adduct as a pure compound. LRMS: +ve ion 581 [M+Na], HPLC: RT=5.49 min, 100% pure.

The compounds of Examples **88a-93** were prepared by the synthetic route outlined in Scheme 9 and as described in detail for Example 88. Step C and Step D were carried out in parallel format for all examples. Characterisation data for the compounds are provided in Table 7.

Table 7			
Example	Structure	Mass Spectral · Data	HPLC RT(min)
88		581 (M+Na), 559 (M+1), 557 (M-1).	5.5
88a		545(M+1), 567(M+Na), 543 (M-1).	5.3
89		601 (M+1), 623 (M+Na), 599 (M-1).	5.4
90		614 (M+1), 636 (M+Na), 612 (M-1).	4.8
91		615 (M+1), 637 (M+Na), 613 (M-1).	5.2
92		615 (M+1), 637 (M+Na), 613 (M-1).	5.4

The compounds of Examples 88a - 93 are named as follows:

Example 88a. 4-(1-{2*S*-[3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-N-methyl benzamide

Example 89. 2*R*-Cyclopentylmethyl-*N*-(2,2-dimethyl-1*S*-{4-[4-(morpholine-4-carbonyl)-phenoxy]-piperidine-1-carbonyl}-propyl)-3-(formyl-hydroxy-amino)-propionamide.

Example 90. 2*R*-Cyclopentylmethyl-*N*-(2,2-dimethyl-1*S*-{4-[4-(4-methyl-piperazine-1-carbonyl)-phenoxy]-piperidine-1-carbonyl}-propyl)-3-(formyl-hydroxy-amino)-propionamide.

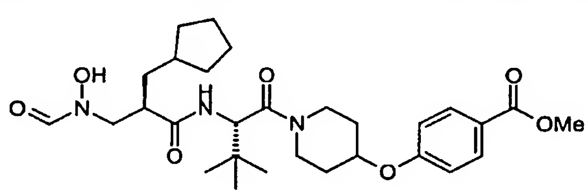
Example 91. 2*R*-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-*N*-(1*S*-{4-[4-(4-hydroxy-piperidine-1-carbonyl)-phenoxy]-piperidine-1-carbonyl}-2,2-dimethyl-propyl)-propionamide.

Example 92. 2*R*-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-*N*-(1*S*-{4-[4-(2*S*-hydroxymethyl-pyrrolidine-1-carbonyl)-phenoxy]-piperidine-1-carbonyl}-2,2-dimethyl-propyl)-propionamide.

Example 93. 4-(1-{2*S*-[2*R*-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-benzoic acid

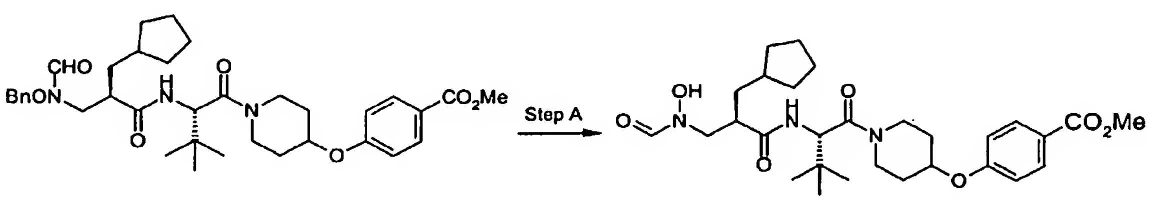
Example 94

4-(1-{2*S*-[2*R*-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-benzoic acid methyl ester



The title compound was prepared as detailed below (see scheme 9) from 4-(1-{2*S*-[3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-benzoic acid methyl ester (scheme 8).

Scheme 9



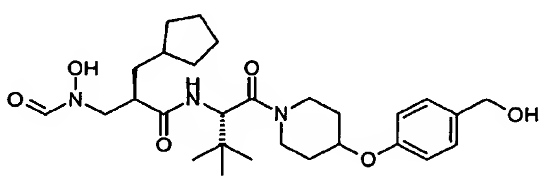
Reagents and conditions: Step A: H_2, Pd/C, EtOH, reflux

To a solution of 4-(1-{2*S*-[3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-benzoic acid methyl ester (80 mg, 0.125 mmol) in EtOH (4 ml) was added Pd/C (10 mg). To the resulting suspension, H_2 was bubbled for 2h. Pd/C was filtered off through a celite pad to give the desired compound in 88% yield.

^{1}H NMR δ ($CDCl_3$), 8.40 (0.3H, s), 7.99 (2H, dd, J_1=3.04 J_2=8.85), 7.81 (0.7H, s), 6.91 (2H, dd, J_1=4.87 J_2=8.84), 6.78 (1H, m), 4.94 (1H, m), 4.64 (1H, m), 3.99 (2H, m), 3.89 (3H, s), 3.75 (2H, m), 3.48 (3H, m), 2.81 (1H, m), 2.10-1.32 (13H, m), 1.08 (2H, bs), 0.97 (9H, m); ^{13}C NMR δ ($CDCl_3$), 175.7, 173.6, 170.3, 167.1, 161.2, 132.1, 123.4, 115.5, 72.3, 58.7, 55.1, 54.8, 52.9, 52.3, 44.2, 43.6, 39.2, 39.1, 38.4, 36.6, 35.8, 33.2, 31.6, 31.2, 27.0, 25.5,

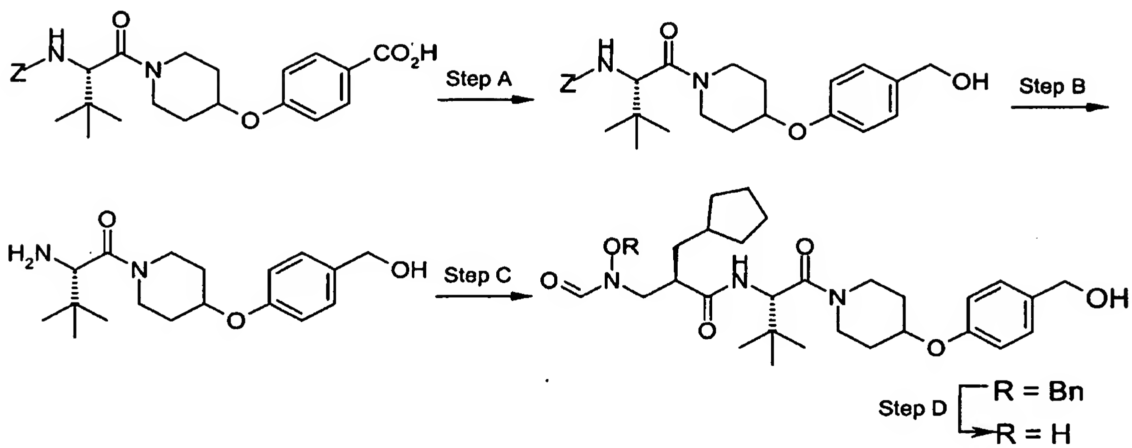
Example 95

2*R*-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-N-{1*S*-[4-(4-hydroxymethyl-phenoxy)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-propionamide



The title compound was prepared as detailed below (see scheme 10) from 4-[1-(2*S*-Benzyloxycarbonylamino-3,3-dimethyl-butyryl)-piperidin-4-yloxy]-benzoic acid

Scheme 10



Reagents and conditions: Step A: BH_3, THF; Step B: H_2, Pd/C, EtOH; Step C: PFP ester, NEt_3 D
Step D: H2, Pd/C, EtOH

Step A: {1*S*-[4-(4-Hydroxymethyl-phenoxy)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid benzyl ester

To a cold (10°C) solution of the 4-[1-(2*S*-Benzyloxycarbonylamino-3,3-dimethyl-butyryl)-piperidin-4-yloxy]-benzoic acid (750 mg, 1.6 mmol) in THF (10 ml) was added dropwise BH_3 The reaction mixture was stirred at room temperature for 12 hours. Water was then added dropwise and the solvent removed under reduced pressure. The crude material was taken-up in EtOAc. After filtration, the organic layer was concentrated to yield a white foam as a pure compound in 93% yield.

^{1}H NMR δ ($CDCl_3$), 7.35-7.28 (7H, m), 6.89 (2H, m), 5.60 (1H, m), 5.15-5.03 (2H, AB system), 4.65-4.48 (3H, m), 3.91-3.51 (5H, m), 1.95-1.25 (4H, m), 1.00 (9H, s). ESMS: +ve ion 477 [M+Na], HPLC: RT=6.3 min, 93% pure.

Step B: 2*S*-Amino-1-[4-(4-hydroxymethyl-phenoxy)-piperidin-1-yl]-3,3-dimethyl-butan-1-one

To a solution of the latter compound (680 mg, 1.49 mmol) in EtOH (10 ml) was added Pd/C (68 mg) and H_2 was bubbled through the resulting suspension for 2 hours. The reaction mixture was then stirred for two hours under a blanket of H_2. Pd/C was then

filtered off through a celite pad. The solvent was removed under reduced pressure to give the desired compound in 94% yield. ^{1}H NMR δ ($CDCl_3$), 7.29-6.86 (4H, AB system), 4.62 (2H, s), 4.55 (1H, m), 3.82-3.58 (2H, m), 1.92-1.73 (11H), 1.00 (9H, s). ESMS: +ve ion 321 [M+1].

Step C: 3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-N-{1*S*-[4-(4-hydroxymethyl-phenoxy)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-propionamide

To a solution of the latter compound, were added PFP ester (635 mg, 1.35 mmol) and NEt_3 (193 ml, 1.41 mmol). The reaction mixture was then stirred for 12 hours. DMF was removed under reduced pressure and the crude material was taken-up in EtOAc, washed with water, sodium carbonate (1N), saturate aqueous solution of NH_4Cl and brine. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification through flash chromatography the desired adduct was obtained as a white foam in 63% yield. ^{1}H NMR; δ ($CDCl_3$), 8.13 (0.25H, m), 7.88 (0.25H, m), 7.38 (5H, s), 7.27 (2.5H, m), 6.87 (2H, m), 6.32 (1H, m), 4.89 (3H, m), 4.56 (3H, m), 3.96 (1H, m), 3.73 (2H, m), 3.45 (1H, m), 2.60 (1H, m), 2.06-1.31 (15H, m), 1.06 (11H, m); ESMS: +ve ion 630 [M+Na], HPLC: RT=6.31 min, 100% pure.

Step D: 2*R*-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-N-{1*S*-[4-(4-hydroxymethyl-phenoxy)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-propionamide

To a solution of the latter compound (50 mg, 0.08 mmol) in MeOH (3 ml) were added HCO_2NH_4 (26 mg, 0.41 mmol) and Pd/C (5 mg). The resulting suspension was stirred for 2 hours. Pd/C was filtered off. The solvent was removed under reduced pressure and the crude material taken-up in EtOAc, washed with water and brine. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield the expected compound in 62% yield. ^{1}H NMR; δ ($CDCl_3$), 8.39 (0.3H, s), 7.81 (0.7H, s), 7.29 (2H, dd, J_1=3.47 J_2=9.11), 6.89 (2H, dd, J_1=3.64 J_2=8.55), 6.73 (1H, m), 4.94 (1H, m), 4.62 (3H, m), 4.01 (2H,m), 3.76 (2H, m), 3.48 (3H, m), 2.74 (1H, m), 2.08-1.35 (19H, m), 1.02 (13H, m); ESMS: +ve ion 540 [M+Na], -ve ion 516 [M-1] HPLC: RT=5.49 min, 100% pure.

Biological Example

Minimal inhibitory concentrations (MIC) of compounds of the invention against *E. coli* strain DH5α (Genotype; F-φ80d*lac*ZΔM15Δ(*lac*ZYA-*arg*F)U169 *deo*R *rec*A1 *end*A1 *hsd*R17(r_K^-, m_K^+)*pho*A *sup*E44λ $^-$ *thi*-1 *gyr*A96 *rel*A1) obtained from GibcoBRL Life Technologies, or *Staphylococcus capitis* (American Type Culture Collection number 35661) were determined as follows. Stock solutions of each test compound were prepared by dissolution of the compound in dimethylsulfoxide at 10mM. For the determination of the minimal inhibitory concentration, two fold serial dilutions were prepared in 2xYT broth (typtone 16g/1, yeast extract 10g/1, sodium chloride 5g/1 obtained from BIO 101 Inc, 1070 Joshua Way, Vista, CA92083, USA) to yield 0.05 ml compound-containing medium per well. Inocula were prepared from cultures grown overnight in 2xYT broth at 37°C. Cell densities were adjusted to absorbance at 660nm (A_{660}) = 0.1; the optical density-standardised preparations were diluted 1:1000 in 2xYT broth; and each well inoculated with 0.05ml of the diluted bacteria. Microtiter plates were incubated at 37°C for 18 hours in a humidified incubator. The MIC (μM) was recorded as the lowest drug concentration that inhibited visible growth.

In general, the compounds of the Examples were more active against the Gram positive *S. capitis* than the Gram negative *E. coli*. Results for some of the compounds of the Examples are reported in Table 8:

Table 8

Example No.	E. Coli MIC (μM)	S. Capitis (μM)
24	>200, <400	100
29	100	>200, <400
44	200	12

50	200	6.2
52	200	6.2
54	200	3.1
55	200	6.2
56	50	25
57	100	6.2
69	200	25
74	200	25
78	>200, <400	200
79	>200, <400	6.25
88	100	6.2
89	200	25
91	200	25

Using the above protocol for establishing the MIC values against *S. capitis*, it appears that in general compounds of the invention of formula (II) wherein Q is a hydroxamate group have activities comparable to compounds of similar structure wherein Q is an N-formylhydroxylamine group.

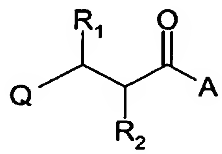
In another experiment, the MICs of the compound of Example 91 were determined against certain respiratory tract pathogens, using the Microdilution Broth Method according to the approved standard of the National Committee for Clinical Laboratory Standards procedure (Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically - Fourth Edition ISBN 1-56238-309-4). The results appear in Table 9.

Table 9

Organism	MIC (μg/ml)
Moraxella catarrhalis 2413	0.25
Moraxella catarrhalis 2412	0.5
Haemophilus Infuenzae 1414	4
Haemophilus Infuenzae 1390	1
Streptococcus pneumoniae (PRP) 2390	0.25
Streptococcus pneumoniae (PIP) 2391	0.25
Streptococcus pneumoniae (PSP) 2403	0.25

Claims:

1. A compound of formula (II), or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof



(II)

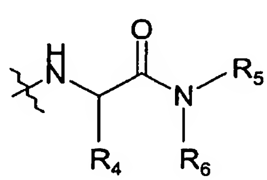
wherein

Q represents a radical of formula -N(OH)CH(=O) or formula -C(=O)NH(OH);

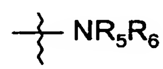
R_1 represents hydrogen, C_1-C_6 alkyl or C_1-C_6 alkyl substituted by one or more halogen atoms, or, except when Q is a radical of formula -N(OH)CH(=O), a hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkenyloxy, amino, C_1-C_6 alkylamino, or di-(C_1-C_6 alkyl)amino group;

R_2 represents a substituted or unsubstituted C_1-C_6 alkyl, cycloalkyl(C_1-C_6 alkyl)- or aryl(C_1-C_6 alkyl)- group;

and A represents a group of formula (IIA), or (IIB):



(IIA)



(IIB)

wherein R_4 represents the side chain of a natural or non-natural alpha amino acid, and R_5 and R_6 when taken together with the nitrogen atom to which they are attached form a saturated heterocyclic first ring of 5 to 7 atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7

atoms; characterised in that

(a) the said second ring is substituted by (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkoxy, hydroxy, mercapto, (C_1-C_6)alkylthio, halo, amino, trifluoromethyl, oxo, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group; and/or

(b) the said first or second ring is substituted by a group of formula (IIC), provided that the first ring is not substituted by phenoxy, benzyl or benzyl substituted by (C_1-C_6)alkyl, (C_1-C_6)alkoxy, phenoxy, hydroxy, mercapto, (C_1-C_6)alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group,

$$-(Alk^1)_m-(X)_p-(Alk^2)_n-Z \qquad \text{(IIC)}$$

wherein
m, p and n are independently 0 or 1;

Z represents, a hydroxy group, or a phenyl or heterocyclic ring of 5 to 7 atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 atoms

Alk^1 and Alk^2 independently represent divalent C_1-C_3 alkylene radicals;

X represents -O-, -S-, -S(O)-, $-S(O_2)-$, -C(=O)-, -NH-, $-NR_7-$ where R_7 is C_1-C_3 alkyl;

and wherein
Alk^1, Alk^2 and Z when Z is not a hydroxy group independently are optionally

substituted by

(C_1-C_6)alkyl, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl,

phenyl, or halophenyl,

trifluoromethyl,

monocyclic 5 or 6-membered hetrocyclic,

benzyl, or halophenylmethyl,

hydroxy, phenoxy, (C_1-C_6)alkoxy, or hydroxy(C_1-C_6)alkyl,

mercapto, (C_1-C_6)alkylthio or mercapto(C_1-C_6)alkyl,

oxo,

nitro,

cyano (-CN)

halo (bromo, chloro, fluoro, or iodo)

-COOH, or $-COOR^A$,

$-CONH_2$, $-CONHR^A$, or $-CONR^AR^B$

$-COR^A$, $-SO_2R^A$,

$-NHCOR^A$,

$-NH_2$, $-NHR^A$, or $-NR^AR^B$,

wherein R^A and R^B are independently a (C_1-C_6) alkyl group, R^A and R^B taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring which may be substituted by (C_1C_3)alkyl, hydroxy, or hydroxy(C_1-C_3)alkyl.

2. A compound as claimed in claim 1 wherein

(a) the said second ring is substituted by (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkoxy, hydroxy, mercapto, (C_1-C_6)alkylthio, amino, trifluoromethyl, oxo, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group; and/or

(b) the said first or second ring is substituted by a group of formula (IIC), provided that the first ring is not substituted by phenoxy, benzyl or benzyl substituted by (C_1-C_6)alkyl, (C_1-C_6)alkoxy, phenoxy, hydroxy, mercapto, (C_1-C_6)alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group,

$$-(Alk^1)_m-(X)_p-(Alk^2)_n-Z \qquad \text{(IIC)}$$

<u>wherein</u>
m, p and n are independently 0 or 1;

Z represents, a hydroxy group, or a phenyl or heterocyclic ring of 5 to 7 atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 atoms

Alk^1 and Alk^2 independently represent divalent C_1-C_3 alkylene radicals;

X represents -O-, -S-, -S(O)-, $-S(O_2)-$, -C(=O)-, -NH-, $-NR_7-$ where R_7 is C_1-C_3 alkyl;

<u>and wherein</u>
Alk^1, Alk^2 and Z when Z is not a hydroxy group independently are optionally substituted by

- (C_1-C_6)alkyl, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl,
- phenyl, or halophenyl,
- trifluoromethyl,
- monocyclic 5 or 6-membered hetrocyclic,
- benzyl,
- hydroxy, phenoxy, or (C_1-C_6)alkoxy,

mercapto, or (C_1-C_6)alkylthio,

oxo,

nitro,

-COOH, or $-COOR^A$,

$-CONH_2$, $-CONHR^A$, or $-CONR^AR^B$

$-COR^A$,

$-NHCOR^A$,

$-NH_2$, $-NHR^A$, or $-NR^AR^B$,

wherein R^A and R^B are independently a (C_1-C_6) alkyl group,

3. A method for the treatment of bacterial infections in humans and non-human mammals, which comprises administering to a subject suffering such infection an antibacterially effective dose of a compound as claimed in claim 1 or claim 2.

4. A method for the treatment of bacterial contamination by applying an antibacterially effective amount of a compound as claimed in claim 1 or claim 2 to the site of contamination.

5. The use of a compound as claimed in claim 1 or claim 2 in the manufacture of an antibacterial composition.

6. A pharmaceutical or veterinary composition comprising a compound as claimed in claim 1 or claim 2 together with a pharmaceutically of veterinarily acceptable carrier.

7. A compound as claimed in claim 1 or claim 2, a method as claimed in claim 3 or claim 4, the use as claimed in claim 5 or a composition as claimed in claim 6 wherein R_1 is hydrogen.

8. A compound, method, use or composition as claimed in claim 7 wherein R_2 is (C_1-C_6)alkyl-, cycloalkylmethyl-, (C_1-C_3)alkyl-S-(C_1-C_3)alkyl-, or (C_1-C_3)alkyl-O-$(C_1-$

C_3)alkyl-.

9. A compound, method, use or composition as claimed in claim 7 wherein R_2 is n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

10. A compound as claimed in claim 1 or claim 2, a method as claimed in claim 3 or claim 4, the use as claimed in claim 5 or a composition as claimed in claim 6 wherein R_4 is

the characterising group of a natural α amino acid, for example benzyl, or 4-methoxyphenylmethyl, in which any functional group may be protected, any amino group may be acylated and any carboxyl group present may be amidated; or

a group -[Alk]$_n$$R_9$ where Alk is a (C_1-C_6)alkylene or (C_2-C_6)alkenylene group optionally interrupted by one or more -O-, or -S- atoms or -N(R_{12})- groups [where R_{12} is a hydrogen atom or a (C_1-C_6)alkyl group], n is 0 or 1, and R_9 is hydrogen or an optionally substituted phenyl, aryl, heterocyclyl, cycloalkyl or cycloalkenyl group or (only when n is 1) R_9 may additionally be hydroxy, mercapto, (C_1-C_6)alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, -$CONH_2$, -$COOR^A$, -$NHCOR^A$, -$CONHR^A$, -NHR^A, -NR^AR^B, or -$CONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group; or

a benzyl group substituted in the phenyl ring by a group of formula -OCH_2COR_8 where R_8 is hydroxyl, amino, (C_1-C_6)alkoxy, phenyl(C_1-C_6)alkoxy, (C_1-C_6)alkylamino, di((C_1-C_6)alkyl)amino, phenyl(C_1-C_6)alkylamino; or

a heterocyclic(C_1-C_6)alkyl group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, (C_1-C_6)alkoxy, cyano, (C_1-C_6)alkanoyl, trifluoromethyl (C_1-C_6)alkyl, hydroxy, formyl, amino,

$(C_1$-$C_6)$alkylamino, di-$(C_1$-$C_6)$alkylamino, mercapto, $(C_1$-$C_6)$alkylthio, hydroxy$(C_1$-$C_6)$alkyl, mercapto$(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$alkylphenylmethyl; or

a group -$CR_aR_bR_c$ in which:

each of R_a, R_b and R_c is independently hydrogen, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, phenyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl; or

R_c is hydrogen and R_a and R_b are independently phenyl or heteroaryl such as pyridyl; or

R_c is hydrogen, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, phenyl$(C_1$-$C_6)$alkyl, or $(C_3$-$C_8)$cycloalkyl, and R_a and R_b together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

R_a, R_b and R_c together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

R_a and R_b are each independently $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, phenyl$(C_1$-$C_6)$alkyl, or a group as defined for R_c below other than hydrogen, or R_a and R_b together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and R_c is hydrogen, -OH, -SH, halogen, -CN, -CO_2H, $(C_1$-$C_4)$perfluoroalkyl, -CH_2OH, -$CO_2(C_1$-$C_6)$alkyl, -$O(C_1$-$C_6)$alkyl, -$O(C_2$-$C_6)$alkenyl, -$S(C_1$-$C_6)$alkyl, -$SO(C_1$-$C_6)$alkyl, -$SO_2(C_1$-$C_6)$ alkyl, -$S(C_2$-$C_6)$alkenyl, -$SO(C_2$-$C_6)$alkenyl, -$SO_2(C_2$-$C_6)$alkenyl or a group -Q-W wherein Q represents a bond or -O-, -S-, -SO- or -SO_2- and W represents a phenyl, phenylalkyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_8)$cycloalkylalkyl, $(C_4$-$C_8)$cycloalkenyl, $(C_4$-$C_8)$cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, -

CO_2H, $-CO_2(C_1-C_6)$alkyl, $-CONH_2$, $-CONH(C_1-C_6)$alkyl, $-CONH(C_1-C_6$alkyl$)_2$, -CHO, $-CH_2OH$, (C_1-C_4)perfluoroalkyl, $-O(C_1-C_6)$alkyl, $-S(C_1-C_6)$alkyl, $-SO(C_1-C_6)$alkyl, $-SO_2(C_1-C_6)$alkyl, $-NO_2$, $-NH_2$, $-NH(C_1-C_6)$alkyl, $-N((C_1-C_6)$alkyl$)_2$, $-NHCO(C_1-C_6)$alkyl, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, phenyl or benzyl.

11. A compound, method, use or composition as claimed in claim 9 or claim 10 wherein R_4 is methyl, ethyl, n-propyl, n-butyl, benzyl, 4-chlorobenzyl, 4-hydroxybenzyl, phenyl, cyclohexyl, cyclohexylmethyl, pyridin-3-ylmethyl, tert-butoxymethyl, naphthylmethyl, iso-butyl, sec-butyl, tert-butyl, 1-benzylthio-1-methylethyl, 1-methylthio-1-methylethyl, 1-mercapto-1-methylethyl, 1-methoxy-1-methylethyl, 1-hydroxy-1-methylethyl, 1-fluoro-1-methylethyl, hydroxymethyl, 2-hydroxethyl, 2-carboxyethyl, 2-methylcarbamoylethyl, 2-carbamoylethyl, or 4-aminobutyl.

12. A compound, method, use or composition as claimed in claim 9 or claim 10 wherein R_4 is tert-butyl, iso-butyl, benzyl, isopropyl or methyl.

13. A compound, method, use or composition as claimed in claim 12 wherein R_5 and R_6 taken together with the nitrogen atom to which they are attached form a piperidin-1-yl or 1-piperazin-4-yl ring.

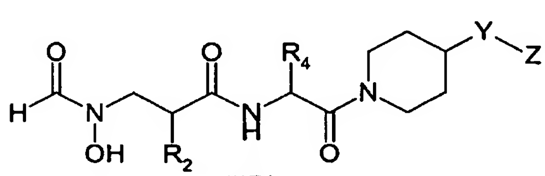
14. A compound, method, use or composition as claimed in any of claims 9, 12 or 13 wherein the substituent (IIC) has the formula $-CH_2Z$, -OZ, or -(C=O)Z wherein Z is as defined in claim 1 or claim 2

15. A compound, method, use or composition as claimed in any of claims 9 or 12-14 wherein in the substituent (IIC) Z is a phenyl, 3,4-methylenedioxyphenyl, morpholinyl, pyrimidinyl, 1,2,3-thiadiazolyl, 1,4-thiazolyl, benzofuranyl, furanyl, thienyl, pyranyl, pyrrolyl, pyrazolyl, isoxazolyl, or pyridyl ring which may optionally be substituted as specified in the definition of Z in claim 1 or claim 2

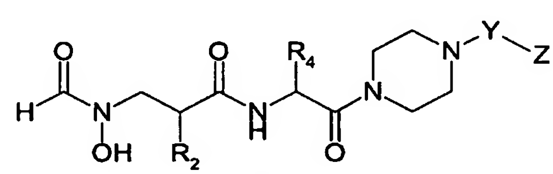
16. A compound, method, use or composition as claimed in any of claims 9 or 12-14 wherein in the substituent (IIC) Z is a phenyl, 3,4-methylenedioxyphenyl, morpholinyl, pyrimidin-2-yl, 1,2,3-thiadiazol-5-yl, 1,4-thiazol-5-yl, benzofuran-2-yl, 2- or 3-furanyl, 2- or 3-thienyl, 2- or 3-pyranyl, 2-, 3- or 4-pyrrolyl, 3-, 4- or 5-pyazolyl, 3-, 4- or 5-isoxazolyl, or 2-, 3- or 4-pyridyl ring which may optionally be substituted as specified in the definition of Z in claim 1 or claim 2.

17. A compound as claimed in claim 1, a method as claimed in claim 2 or claim 3, the use as claimed in claim 4 or a composition as claimed in claim 5 wherein R_1 is hydrogen; R_2 is n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl; R_4 is tert-butyl, iso-butyl, benzyl or methyl; R_5 and R_6 taken together with the nitrogen atom to which they are attached form a piperidin-1-yl or 1-piperazin-4-yl ring; the substituent (IIC) has the formula $-CH_2Z$, -OZ, or -(C=O)Z wherein Z is as defined in claim 16 or claim 17.

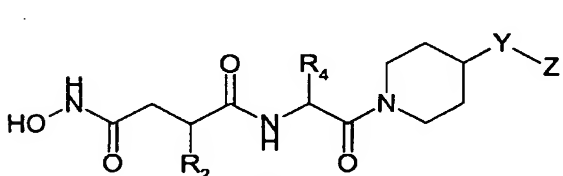
18. A compound as claimed in claim 1 or claim 2, a method as claimed in claim 3 or claim 4, the use as claimed in claim 5 or a composition as claimed in claim 6 wherein the compound is one selected from the group consisting of compounds of formulae (IID) - (IIG) and (IIW) - (IIZ):



(IID)



(IIE)



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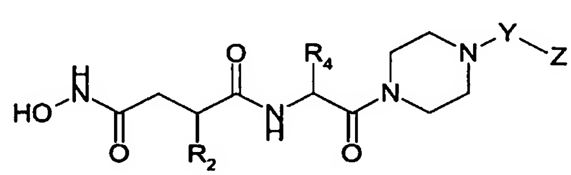

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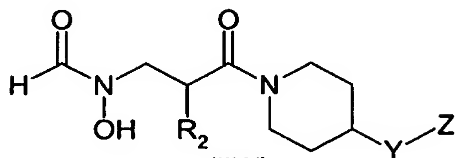
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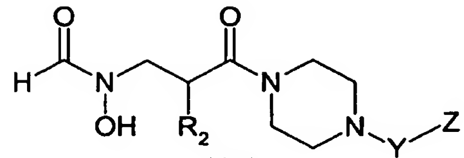
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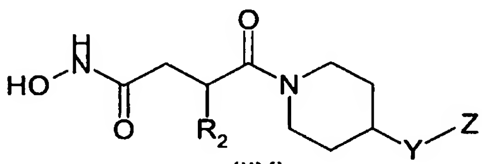
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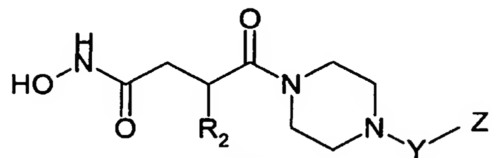
(IIZ)

wherein

R_2 is n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl;

R_4 is tert-butyl, iso-butyl, benzyl or methyl;

Y is $-CH_2-$, -O- or -(C=O)-; and

Z is as defined in claim 16 or 17.

19. A compound as claimed in claim 1 or claim 2, a method as claimed in claim 3 or claim 4, the use as claimed in claim 5 or a composition as claimed in claim 6 wherein the compound is one specifically named and/or exemplified herein, or is the hydroxamate (Q represents a radical of formula -C(=O)NH(OH)) or N-formylhydroxylamine (Q represents a radical of formula -N(OH)CH(=O)) analogue thereof, as the case may be.

20. A compound as claimed in claim 1 or claim 2, a method as claimed in claim 3 or claim 4, the use as claimed in claim 5 or a composition as claimed in claim 6 wherein the compound is *N*-[1*S*-(4-benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-2*R*-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide or *N*-[1*S*-(4-benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-2*R*-cyclopentylmethyl-*N*-hydroxy-succinamide.

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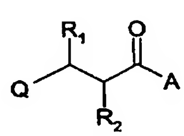

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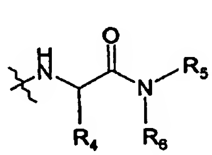

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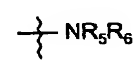

(IIB)

(57) Abstract: Compounds of formula (II) are antibacterial agents wherein Q represents a radical of the formula: -N(OH)CH(=O) or the formula: -C(=O)NH(OH); R_1 represents hydrogen, C_1-C_6 alkyl or C_1-C_6 alkyl substituted by one or more halogen atoms, or, except when Q is a radical of the formula: -N(OH)CH(=O), a hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkenyloxy, amino, C_1-C_6 alkylamino, or di-(C_1-C_6 alkyl)amino group; R_2 represents a substituted or unsubstituted C_1-C_6 alkyl, cycloalkyl(C_1-C_6 alkyl)- or aryl(C_1-C_6 alkyl)- group; and A represents a group of formula (IIA), or (IIB) wherein R_4 represents the side chain of a natural or non-natural alpha amino acid, and R_5 and R_6 when taken together with the nitrogen atom to which they are attached form a saturated heterocyclic first ring of 5 to 7 atoms as specified in the description.

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Antibacterial Agents

This invention relates to novel hydroxamic acid and N-formyl hydroxylamine derivatives having antibacterial activity, to methods of treatment using such compounds, and to pharmaceutical and veterinary compositions comprising such compounds.

Background to the Invention

Many classes of antibacterial agents are known, including the penicillins and cephalosporins, tetracyclines, sulfonamides, monobactams, fluoroquinolones and quinolones, aminoglycosides, glycopeptides, macrolides, polymyxins, lincosamides, trimethoprim and chloramphenicol. The fundamental mechanisms of action of these antibacterial classes vary.

Bacterial resistance to many known antibacterials is a growing problem. Accordingly there is a continuing need in the art for alternative antibacterial agents, especially those which have mechanisms of action fundamentally different from the known classes.

Amongst the Gram-positive pathogens, such as Staphylococci, Streptococci, Mycobacteria and Enterococci, resistant strains have evolved/arisen which makes them particularly difficult to eradicate. Examples of such strains are methicillin resistant *Staphylococcus aureus* (MRSA), methicillin resistant coagulase negative Staphylococci (MRCNS), penicillin resistant *Streptococcus pneumoniae* and multiply resistant *Enterococcus faecium.*

Pathogenic bacteria are often resistant to the aminoglycoside, β-lactam (penicillins and cephalosporins), and chloramphenicol types of antibiotic. This resistance involves the enzymatic inactivation of the antibiotic by hydrolysis or by formation of inactive derivatives. The β-lactam (penicillin and cephalosporin) family of antibiotics are characterised by the presence of a β-lactam ring structure. Resistance to this

family of antibiotics in clinical isolates is most commonly due to the production of a "penicillinase" (β-lactamase) enzyme by the resistant bacterium which hydrolyses the β-lactam ring thus eliminating its antibacterial activity.

Recently there has been an emergence of vancomycin-resistant strains of enterococci (Woodford N. 1998 Glycopeptide-resistant enterococci: a decade of experience. Journal of Medical Microbiology. 47(10):849-62). Vancomycin-resistant enterococci are particularly hazardous in that they are frequent causes of hospital based infections and are inherently resistant to most antibiotics. Vancomycin works by binding to the terminal D-Ala-D-Ala residues of the cell wall peptidioglycan precursor. The high-level resistance to vancomycin is known as VanA and is conferred by a genes located on a transposable element which alter the terminal residues to D-Ala-D-lac thus reducing the affinity for vancomycin.

In view of the rapid emergence of multidrug-resistant bacteria, the development of antibacterial agents with novel modes of action that are effective against the growing number of resistant bacteria, particularly the vancomycin resistant enterococci and β-lactam antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus*, is of utmost importance.

Brief Description of the Invention

This invention is based on the finding that certain hydroxamic acid and N-formyl hydroxylamine derivatives have antibacterial activity, and makes available a new group of antibacterial agents. It has been found that the compounds with which this invention is concerned are antibacterial with respect to a range of bacteria, with potency against Gram-positive organisms generally being greater than against Gram-negatives. Many of the compounds of the invention show activity against bacteria responsible for respratory infections, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.

Although it may be of interest to establish the mechanism of action of the

compounds with which the invention is concerned, it is their ability to inhibit bacterial growth that makes them useful. However, it is presently believed that their antibacterial activity is due, at least in part, to intracellular inhibition of bacterial polypeptide deformylase (PDF; EC 3.5.1.31).

All ribosome-mediated synthesis of proteins starts with a methionine residue. In prokaryotes the methionyl moiety carried by the initiator tRNA is N-formylated prior to its incorporation into a polypeptide. Consequently, N-formylmethionine is always present at the N-terminus of a nascent bacterial polypeptide. However, most mature proteins do not retain the N-formyl group or the terminal methionine residue. Deformylation is required prior to methionine removal, since methionine aminopeptidase does not recognise peptides with an N-terminal formylmethionine residue (Solbiati et al., J. Mol. Biol. 290:607-614, 1999). Deformylation is, therefore, a crucial step in bacterial protein biosynthesis and the enzyme responsible, PDF, is essential for normal bacterial growth. Although the gene encoding PDF (*def*) is present in all pathogenic bacteria for which sequences are known (Meinnel et al., J. Mol. Biol, 266:939-49, 1997), it has no eukaryotic counterpart, making it an attractive target for antibacterial chemotherapy.

The isolation and characterisation of PDF has been facilitated by an understanding of the importance of the metal ion in the active site (Groche et al., Biophys. Biochem. Res. Commun., 246:324-6, 1998). The Fe^{2+} form is highly active *in vivo* but is unstable when isolated due to oxidative degradation (Rajagopalan et al., J. Biol. Chem. 273:22305-10, 1998). The Ni^{2+} form of the enzyme has specific activity comparable with the ferrous enzyme but is oxygen-insensitive (Ragusa et al., J. Mol. Biol. 1998, 280:515-23, 1998). The Zn^{2+} enzyme is also stable but is almost devoid of catalytic activity (Rajagopalan et al., J. Am. Chem. Soc. 119:12418-12419, 1997).

Several X-ray crystal structures and NMR structures of *E. coli* PDF, with or without bound inhibitors, have been published (Chan et al., Biochemistry 36:13904-9, 1997; Becker et al., Nature Struct. Biol. 5:1053-8, 1998; Becker et al., J. Biol. Chem.

273:11413-6, 1998; Hao et al., Biochemistry, 38:4712-9, 1999; Dardel et al., J. Mol. Biol. 280:501-13, 1998; O'Connell et al., J. Biomol. NMR, 13:311-24, 1999), indicating similarities in active site geometry to metalloproteinases such as thermolysin and the metzincins.

Recently the substrate specificity of PDF has been extensively studied (Ragusa et al., J. Mol. Biol. 289:1445-57, 1999; Hu et al., Biochemistry 38:643-50, 1999; Meinnel et al., Biochemistry, 38:4287-95, 1999). These authors conclude that an unbranched hydrophobic chain is preferred at P1', while a wide variety of P2' substituents are acceptable and an aromatic substituent may be advantageous at the P3' position. There have also been reports that small peptidic compounds containing an H-phosphonate (Hu et al., Bioorg. Med. Chem. Lett., 8:2479-82, 1998) or thiol (Meinnel et al., Biochemistry, 38:4287-95, 1999) metal binding group are micromolar inhibitors of PDF. Peptide aldehydes such as calpeptin (N-Cbz-Leu-norleucinal) have also been shown to inhibit PDF (Durand et al., Arch. Biochem. Biophys., 367:297-302, 1999). However, the identity of the metal binding group and its spacing from the rest of the molecule ("recognition fragment") has not been studied extensively. Furthermore, non-peptidic PDF inhibitors, which may be desirable from the point of view of bacterial cell wall permeability or oral bioavailability in the host species, have not been identified.

Related Prior Art

Certain N-formyl hydroxylamine derivatives have previously been claimed in the patent publications listed below, although very few examples of such compounds have been specifically made and described:

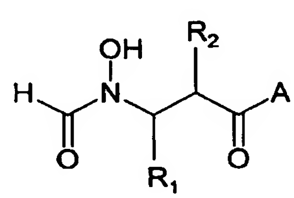
EP-B-0236872	(Roche)
WO 92/09563	(Glycomed)
WO 92/04735	(Syntex)
WO 95/19965	(Glycomed)
WO 95/22966	(Sanofi Winthrop)

WO 95/33709	(Roche)
WO 96/23791	(Syntex)
WO 96/16027	(Syntex/Agouron)
WO 97/03783	(British Biotech)
WO 97/18207	(DuPont Merck)
WO 98/38179	(GlaxoWellcome)
WO 98/47863	(Labs Jaques Logeais)

The pharmaceutical utility ascribed to the N-formyl hydroxylamine derivatives in those publications is the ability to inhibit matrix metalloproteinases (MMPs) and in some cases release of tumour necrosis factor (TNF), and hence the treatment of diseases or conditions mediated by those enzymes, such as cancer and rheumatoid arthritis.

In addition to these, US-A-4,738,803 (Roques et al.) also discloses N-formyl hydroxylamine derivatives, however, these compounds are disclosed as enkephalinase inhibitors and are proposed for use as antidepressants and hypotensive agents. Also, WO 97/38705 (Bristol-Myers Squibb) discloses certain N-formyl hydroxylamine derivatives as enkephalinase and angiotensin converting enzyme inhibitors.

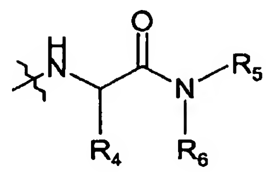
Our copending International Patent Application No. WO 99/39704 describes and claims, *inter alia*, the use of a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof in the preparation of an antibacterial composition:



(I)

wherein R_1 represents hydrogen, C_1-C_6 alkyl or C_1-C_6 alkyl substituted by one or more halogen atoms; R_2 represents a substituted or unsubstituted C_1-C_6 alkyl,

cycloalkyl(C_1-C_6 alkyl)- or aryl(C_1-C_6 alkyl)- group; and A represents a group of formula (IA), or (IB):



(IA)

(IB)

wherein R_4 represents the side chain of a natural or non-natural alpha amino acid, and R_5 and R_6 when taken together with the nitrogen atom to which they are attached form an optionally substituted saturated heterocyclic ring of 3 to 8 atoms which ring is optionally fused to a carbocyclic or second heterocyclic ring.

Very many hydroxamic acid derivatives are known. Many have been disclosed as having matrix metalloproteinase (MMP) inhibitory activity, and thus to be potentially useful for the treatment of diseases mediated by MMPs, for example cancer, arthritides, and conditions involving tissue remodeling such as wound healing, and restenosis. In addition our International Patent Application No. WO 99/59568 describes the use of analogues of the N-formylhydroxylamine derivatives of WO 99/39704 (wherein the N-formylhydroxylamine group is replaced by a hydroxamic acid group) in the preparation of an antibacterial composition.

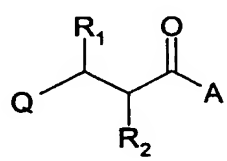
Brief Description of the Invention

This invention relates to a group of antibacterially active hydroxamic acid and and N-formyl hydroxylamine compounds which differ in structure from those of International Patent Applications Nos. WO 99/59568 and WO 99/39704, principally in the nature of the -NR_5R_6 group (see formulae (I), (IA) and (IB) above and the hydroxamic acid analogues thereof). In those applications, the term "optionally substituted" as used in relation to the saturated heterocyclic ring formed by R_5, R_6 and the nitrogen to which they are attached is defined as meaning certain specific substituents. In the present

compounds, the group $-NR_5R_6$ is also an optionally substituted saturated heterocyclic ring of 3 to 8 atoms which ring is optionally fused to a carbocyclic or second heterocyclic ring, but the substituents are different from those permitted by WO 99/59568 and WO 99/39704. The group $-NR_5R_6$ of the N-formyl hydroxylamines and hydroxamic acids of the invention is also believed to distinguish the present compounds from those known in the MMP, TNF, ACE, and enkephalinase inhibitor art.

Detailed description of the invention

The present invention provides a compound of formula (II), or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof



(II)

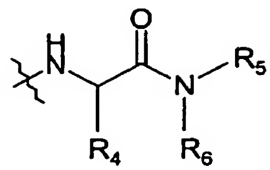
wherein

Q represents a radical of formula -N(OH)CH(=O) or formula -C(=O)NH(OH);

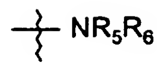
R_1 represents hydrogen, C_1-C_6 alkyl or C_1-C_6 alkyl substituted by one or more halogen atoms, or, except when Q is a radical of formula -N(OH)CH(=O), a hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkenyloxy, amino, C_1-C_6 alkylamino, or di-(C_1-C_6 alkyl)amino group;

R_2 represents a substituted or unsubstituted C_1-C_6 alkyl, cycloalkyl(C_1-C_6 alkyl)- or aryl(C_1-C_6 alkyl)- group;

and A represents a group of formula (IIA), or (IIB):



(IIA)



(IIB)

wherein R_4 represents the side chain of a natural or non-natural alpha amino acid, and R_5 and R_6 when taken together with the nitrogen atom to which they are attached form a saturated heterocyclic first ring of 5 to 7 atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 atoms; characterised in that

(a) the said second ring is substituted by (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkoxy, hydroxy, mercapto, (C_1-C_6)alkylthio, halo, amino, trifluoromethyl, oxo, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group; and/or

(b) the said first or second ring is substituted by a group of formula (IIC), provided that the first ring is not substituted by phenoxy, benzyl or benzyl substituted by (C_1-C_6)alkyl, (C_1-C_6)alkoxy, phenoxy, hydroxy, mercapto, (C_1-C_6)alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group,

$$-(Alk^1)_m-(X)_p-(Alk^2)_n-Z \qquad \text{(IIC)}$$

wherein

m, p and n are independently 0 or 1;

Z represents, a hydroxy group, or a phenyl or heterocyclic ring of 5 to 7 atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 atoms

Alk^1 and Alk^2 independently represent divalent C_1-C_3 alkylene radicals;

X represents -O-, -S-, -S(O)-, -S(O_2)-, -C(=O)-, -NH-, -NR_7- where R_7 is C_1-C_3 alkyl;

<u>and wherein</u>
Alk^1, Alk^2 and Z when Z is not a hydroxy group independently are optionally substituted by

- (C_1-C_6)alkyl, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl,
- phenyl, or halophenyl,
- trifluoromethyl,
- monocyclic 5 or 6-membered hetrocyclic,
- benzyl, or halophenylmethyl,
- hydroxy, phenoxy, (C_1-C_6)alkoxy, or hydroxy(C_1-C_6)alkyl,
- mercapto, (C_1-C_6)alkylthio or mercapto(C_1-C_6)alkyl,
- oxo,
- nitro,
- cyano (-CN)
- halo (bromo, chloro, fluoro, or iodo)
- -COOH, or -$COOR^A$,
- -$CONH_2$, -$CONHR^A$, or -$CONR^AR^B$
- -COR^A, -SO_2R^A,
- -$NHCOR^A$,
- -NH_2, -NHR^A, or -NR^AR^B,

  wherein R^A and R^B are independently a (C_1-C_6) alkyl group, R^A and R^B taken together with the nitrogen atom to which they are attached form a 5- or 6-

membered heterocyclic ring which may be substituted by (C_1C_3)alkyl, hydroxy, or hydroxy$(C_1\text{-}C_3)$alkyl.

A subset of compounds of the invention consists of those of formula (II) as defined above wherein :

(a) the said second ring is substituted by $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkoxy, hydroxy, mercapto, $(C_1\text{-}C_6)$alkylthio, amino, trifluoromethyl, oxo, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a $(C_1\text{-}C_6)$alkyl group; and/or

(b) the said first or second ring is substituted by a group of formula (IIC), provided that the first ring is not substituted by phenoxy, benzyl or benzyl substituted by $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, phenoxy, hydroxy, mercapto, $(C_1\text{-}C_6)$alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a $(C_1\text{-}C_6)$alkyl group,

$$-(Alk^1)_m-(X)_p-(Alk^2)_n-Z \qquad \text{(IIC)}$$

<u>wherein</u>

m, p and n are independently 0 or 1;

Z represents, a hydroxy group, or a phenyl or heterocyclic ring of 5 to 7 atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 atoms

Alk^1 and Alk^2 independently represent divalent $C_1\text{-}C_3$ alkylene radicals;

X represents -O-, -S-, -S(O)-, -S(O_2)-, -C(=O)-, -NH-, -NR_7- where R_7 is C_1-C_3 alkyl;

and wherein

Alk[1], Alk[2] and Z when Z is not a hydroxy group independently are optionally substituted by

(C_1-C_6)alkyl, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl,
phenyl, or halophenyl,
trifluoromethyl,
monocyclic 5 or 6-membered hetrocyclic,
benzyl,
hydroxy, phenoxy, or (C_1-C_6)alkoxy,
mercapto, or (C_1-C_6)alkylthio,
oxo,
nitro,
-COOH, or -$COOR^A$,
-$CONH_2$, -$CONHR^A$, or -$CONR^AR^B$
-COR^A,
-$NHCOR^A$,
-NH_2, -NHR^A, or -NR^AR^B,

wherein R^A and R^B are independently a (C_1-C_6) alkyl group,

In another aspect, the invention provides a method for the treatment of bacterial infections in humans and non-human mammals, which comprises administering to a subject suffering such infection an antibacterially effective dose of a compound of formula (II) as defined above.

In a further aspect of the invention there is provided a method for the treatment of bacterial contamination by applying an antibacterially effective amount of a compound of formula (II) as defined above to the site of contamination.

The compounds of formula (II) as defined above may be used as component(s) of

antibacterial cleaning or disinfecting materials.

On the hypothesis that the compounds (II) act by inhibition of intracellular PDF, the most potent antibacterial effect may be achieved by using compounds which efficiently pass through the bacterial cell wall. Thus, compounds which are highly active as inhibitors of PDF in vitro and which penetrate bacterial cells are preferred for use in accordance with the invention. It is to be expected that the antibacterial potency of compounds which are potent inhibitors of the PDF enzyme in vitro, but are poorly cell penetrant, may be improved by their use in the form of a prodrug, ie a structurally modified analogue which is converted to the parent molecule of formula (II), for example by enzymic action, after it has passed through the bacterial cell wall.

As used herein the term "(C_1-C_6)alkyl" means a straight or branched chain alkyl moiety having from 1 to 6 carbon atoms, including for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein the term "divalent (C_1-C_3)alkylene radical" means a saturated hydrocarbon chain having from 1 to 3 carbon atoms and two unsatisfied valencies.

As used herein the term "(C_2-C_6)alkenyl" means a straight or branched chain alkenyl moiety having from 2 to 6 carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. The term includes, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "C_2-C_6 alkynyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As used herein the term "cycloalkyl" means a saturated alicyclic moiety having from

3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the term "heteroaryl" refers to a 5- or 6- membered aromatic ring containing one or more heteroatoms;. Illustrative of such groups are thienyl, furyl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in particular means a 5-7 membered aromatic or non-aromatic heterocyclic ring containing one or more heteroatoms selected from S, N and O, including for example, pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, morpholinyl, benzofuranyl, pyranyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, maleimido and succinimido groups.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four substituents, each of which independently may be $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxy, mercapto, $(C_1\text{-}C_6)$alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a $(C_1\text{-}C_6)$alkyl group

As used herein the terms "side chain of a natural alpha-amino acid" and "side chain of a non-natural alpha-amino acid" mean the group R^x in respectively a natural and non-natural amino acid of formula $NH_2\text{-}CH(R^x)\text{-}COOH$.

Examples of side chains of natural alpha amino acids include those of alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, histidine, 5-

hydroxylysine, 4-hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, α-aminoadipic acid, α-amino-n-butyric acid, 3,4-dihydroxyphenylalanine, homoserine, α-methylserine, ornithine, pipecolic acid, and thyroxine.

In natural alpha-amino acid side chains which contain functional substituents, for example amino, carboxyl, hydroxy, mercapto, guanidyl, imidazolyl, or indolyl groups as in arginine, lysine, glutamic acid, aspartic acid, tryptophan, histidine, serine, threonine, tyrosine, and cysteine, such functional substituents may optionally be protected.

Likewise, in the side chains of non-natural alpha amino acids which contain functional substituents, for example amino, carboxyl, hydroxy, mercapto, guanidyl, imidazolyl, or indolyl groups, such functional substituents may optionally be protected.

The term "protected" when used in relation to a functional substituent in a side chain of a natural or non-natural alpha-amino acid means a derivative of such a substituent which is substantially non-functional. The widely used handbook by T. W. Greene and P. G. Wuts "Protective Groups in Organic Synthesis" Second Edition, Wiley, New York, 1991 reviews the subject. For example, carboxyl groups may be esterified (for example as a C_1-C_6 alkyl ester), amino groups may be converted to amides (for example as a $NHCOC_1$-C_6 alkyl amide) or carbamates (for example as an $NHC(=O)OC_1$-C_6 alkyl or $NHC(=O)OCH_2Ph$ carbamate), hydroxyl groups may be converted to ethers (for example an OC_1-C_6 alkyl or a $O(C_1$-C_6 alkyl)phenyl ether) or esters (for example a $OC(=O)C_1$-C_6 alkyl ester) and thiol groups may be converted to thioethers (for example a tert-butyl or benzyl thioether) or thioesters (for example a $SC(=O)C_1$-C_6 alkyl thioester).

There are several actual or potential chiral centres in the compounds according to the invention because of the presence of asymmetric carbon atoms. The presence

of several asymmetric carbon atoms gives rise to a number of diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such diastereoisomers and mixtures thereof. Currently, the preferred stereoconfiguration of the carbon atom carrying the R_2 group is R; that of the carbon atom carrying the R_4 group (when asymmetric) is S; and that of the carbon atom carrying the R_1 group (when asymmetric) is R.

In the compounds of the invention:

R_1 may be, for example, hydrogen, methyl, or trifuoromethyl. Hydrogen is currently preferred.

R_2 may be, for example:

optionally substituted C_1-C_8 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl or cycloalkyl;

phenyl(C_1-C_6 alkyl)-, phenyl(C_3-C_6 alkenyl)- or phenyl(C_3-C_6 alkynyl)- optionally substituted in the phenyl ring;

cycloalkyl(C_1-C_6 alkyl)-, cycloalkyl(C_3-C_6 alkenyl)- or cycloalkyl(C_3-C_6 alkynyl)- optionally substituted in the cycloalkyl ring;

heterocyclyl(C_1-C_6 alkyl)-, heterocyclyl(C_3-C_6 alkenyl)- or heterocyclyl(C_3-C_6 alkynyl)- optionally substituted in the heterocyclyl ring; or

$CH_3(CH_2)_pO(CH_2)_q$- or $CH_3(CH_2)_pS(CH_2)_q$-, wherein p is 0, 1, 2 or 3 and q is 1, 2 or 3.

Specific examples of R_2 groups include

methyl, ethyl, n- and iso-propyl, n- and iso-butyl, n-pentyl, iso-pentyl 3-methyl-but-1-yl, n-hexyl, n-heptyl, n-acetyl, n-octyl, methylsulfanylethyl, ethylsulfanylmethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-ethoxymethyl, 3-

hydroxypropyl, allyl, 3-phenylprop-3-en-1-yl, prop-2-yn-1-yl, 3-phenylprop-2-yn-1-yl, 3-(2-chlorophenyl)prop-2-yn-1-yl, but-2-yn-1-yl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, furan-2-ylmethyl, furan-3-methyl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-2-ylmethyl, piperidinylmethyl, phenylpropyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, benzyl, 4-chlorobenzyl, 4-methylbenzyl, and 4-methoxybenzyl.

Presently preferred groups at R_2 are (C_1-C_6)alkyl-, cycloalkylmethyl-, (C_1-C_3)alkyl-S-(C_1-C_3)alkyl-, or (C_1-C_3)alkyl-O-(C_1-C_3)alkyl-, especially n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

R_4 may be, for example

the characterising group of a natural α amino acid, for example benzyl, or 4-methoxyphenylmethyl, in which any functional group may be protected, any amino group may be acylated and any carboxyl group present may be amidated; or

a group $-[Alk]_nR_9$ where Alk is a (C_1-C_6)alkylene or (C_2-C_6)alkenylene group optionally interrupted by one or more -O-, or -S- atoms or $-N(R_{12})-$ groups [where R_{12} is a hydrogen atom or a (C_1-C_6)alkyl group], n is 0 or 1, and R_9 is hydrogen or an optionally substituted phenyl, aryl, heterocyclyl, cycloalkyl or cycloalkenyl group or (only when n is 1) R_9 may additionally be hydroxy, mercapto, (C_1-C_6)alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, -$CONH_2$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group; or

a benzyl group substituted in the phenyl ring by a group of formula -OCH_2COR_8 where R_8 is hydroxyl, amino, (C_1-C_6)alkoxy, phenyl(C_1-C_6)alkoxy,

$(C_1\text{-}C_6)$alkylamino, di($(C_1\text{-}C_6)$alkyl)amino, phenyl$(C_1\text{-}C_6)$alkylamino; or

a heterocyclic$(C_1\text{-}C_6)$alkyl group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, $(C_1\text{-}C_6)$alkoxy, cyano, $(C_1\text{-}C_6)$alkanoyl, trifluoromethyl $(C_1\text{-}C_6)$alkyl, hydroxy, formyl, amino, $(C_1\text{-}C_6)$alkylamino, di-$(C_1\text{-}C_6)$alkylamino, mercapto, $(C_1\text{-}C_6)$alkylthio, hydroxy$(C_1\text{-}C_6)$alkyl, mercapto$(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkylphenylmethyl; or

a group $-CR_aR_bR_c$ in which:

each of R_a, R_b and R_c is independently hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, phenyl$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl; or

R_c is hydrogen and R_a and R_b are independently phenyl or heteroaryl such as pyridyl; or

R_c is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, phenyl$(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_8)$cycloalkyl, and R_a and R_b together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

R_a, R_b and R_c together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

R_a and R_b are each independently $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, phenyl$(C_1\text{-}C_6)$alkyl, or a group as defined for R_c below other than hydrogen, or R_a and R_b together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and R_c is hydrogen, -OH, -SH, halogen, -CN, $-CO_2H$, $(C_1\text{-}C_4)$perfluoroalkyl, $-CH_2OH$, $-CO_2(C_1\text{-}C_6)$alkyl, $-O(C_1\text{-}C_6)$alkyl, $-O(C_2\text{-}C_6)$alkenyl, $-S(C_1\text{-}C_6)$alkyl, $-SO(C_1\text{-}C_6)$alkyl, $-SO_2(C_1\text{-}C_6)$ alkyl, $-S(C_2\text{-}C_6)$alkenyl, $-SO(C_2\text{-}C_6)$alkenyl, $-SO_2(C_2\text{-}C_6)$alkenyl or a group -Q-W wherein Q represents a

bond or -O-, -S-, -SO- or $-SO_2-$ and W represents a phenyl, phenylalkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkylalkyl, (C_4-C_8)cycloalkenyl, (C_4-C_8)cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, $-CO_2H$, $-CO_2(C_1-C_6)$alkyl, $-CONH_2$, $-CONH(C_1-C_6)$alkyl, $-CONH(C_1-C_6alkyl)_2$, -CHO, $-CH_2OH$, (C_1-C_4)perfluoroalkyl, $-O(C_1-C_6)$alkyl, $-S(C_1-C_6)$alkyl, $-SO(C_1-C_6)$alkyl, $-SO_2(C_1-C_6)$alkyl, $-NO_2$, $-NH_2$, $-NH(C_1-C_6)$alkyl, $-N((C_1-C_6)alkyl)_2$, $-NHCO(C_1-C_6)$alkyl, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, phenyl or benzyl.

Examples of particular R_4 groups include methyl, ethyl, benzyl, 4-chlorobenzyl, 4-hydroxybenzyl, phenyl, cyclohexyl, cyclohexylmethyl, pyridin-3-ylmethyl, tert-butoxymethyl, naphthylmethyl, iso-butyl, sec-butyl, tert-butyl, 1-benzylthio-1-methylethyl, 1-methylthio-1-methylethyl, 1-mercapto-1-methylethyl, 1-methoxy-1-methylethyl, 1-hydroxy-1-methylethyl, 1-fluoro-1-methylethyl, hydroxymethyl, 2-hydroxethyl, 2-carboxyethyl, 2-methylcarbamoylethyl, 2-carbamoylethyl, and 4-aminobutyl. Presently preferred R_4 groups include tert-butyl, iso-butyl, benzyl, isopropyl and methyl.

R_5 and R_6 taken together with the nitrogen atom to which they are attached form a saturated 5- to 7-membered monocyclic N-heterocyclic first ring which is attached via the N atom, and which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 atoms. One or more additional ring hetero atoms such as nitrogen may be present in the first ring. Examples of such first rings are 1-pyrrolidinyl, piperidin-1-yl, 1-piperazinyl, hexahydro-1-pyridazinyl, morpholin-4-yl, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-thiazin-4-yl 1-oxide, tetrahydro-1,4-thiazin-4-yl 1,1-dioxide, hexahydroazipino, thiomorpholino, diazepino, thiazolidinyl or octahydroazocino. Presently preferred are piperidin-1-yl and 1-piperazinyl. The substituent (IIC) may be present on a ring carbon atom or a ring nitrogen atom of the first or second rings.

In the substituent (IIC) (from whose definition benzyl, certain substituted benzyls, and phenoxy are excluded) Alk^1 and Alk^2 may independently represent, for example $-(CH_2)-$ or $-(CH_2CH_2)-$. In the case where m is 0 and p is 1, X may be, for example -C(=O)- or $-S(O_2)-$. In such cases n may be 0 or 1, and when the $-NR_5R_6$ first ring contains a second ring nitrogen, the -C(=O)- or $-S(O_2)-$ of (IIC) may be linked to that ring nitrogen in an amide or sulphonamide bond.

In the substituent (IIC) m, n and p may all be 0, so that the group Z is directly linked to the $-NR_5R_6$ first ring.

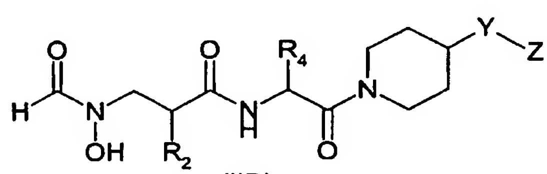
In a preferred subset of the compounds of the invention, the substituent (IIC) has the formula $-CH_2Z$, -OZ, or -(C=O)Z wherein (subject to the exclusion of benzyl, certain substituted benzyls, and phenoxy) Z is a phenyl, 3,4-methylenedioxyphenyl, morpholinyl, pyrimidinyl, 1,2,3-thiadiazolyl, 1,4-thiazolyl, benzofuranyl, furanyl, thienyl, pyranyl, pyrrolyl, pyrazolyl, isoxazolyl, or pyridyl ring which may optionally be substituted as specified. In particular, Z may be a phenyl, 3,4-methylenedioxyphenyl, morpholinyl, pyrimidin-2-yl, 1,2,3-thiadiazol-5-yl, 1,4-thiazol-5-yl, benzofuran-2-yl, 2- or 3-furanyl, 2- or 3-thienyl, 2- or 3-pyranyl, 2-, 3- or 4-pyrrolyl, 3-, 4- or 5-pyazolyl, 3-, 4- or 5-isoxazolyl, or 2-, 3- or 4-pyridyl ring any of which may optionally be substituted as specified in the broad description of the compounds of the invention.

In the compounds of formula (II) as defined above wherein Q is a radical of formula -C(=O)NH(OH) the radicals R_1, R_2, and A may be any of those discussed ubove in relation to compounds (II) wherein Q is a radical of formula -N(OH)CH(=O). However, in addition, R_1 may be, for example, a hydroxy, methoxy, ethoxy, n-propyloxy, allyloxy, amino, methylamino, dimethylamino, ethylamino, or diethylamino group.

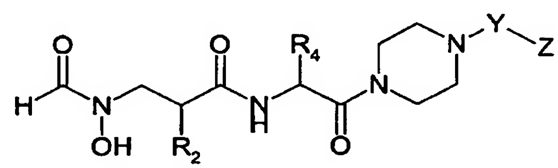
Specific examples of substituents (IIC) include those present in the compounds specifically named, and/or exemplified herein.

Examples of specific compounds of the invention are those of the Examples herein. In those Examples, where a compound of formula (II) above wherein Q is an N-formylhydroxylamine radical -N(OH)CH(=O) is disclosed, it is to be understood that the equivalent compound wherein Q is a hydroxamate radical -C(=O)NH(OH) is also a specific compound of the invention, and *vice versa*.

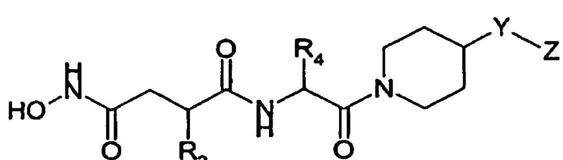
Preferred compounds of the invention include those selected from the group consisting of compounds of formulae (IID) - (IIG) and (IIW) - (IIZ):



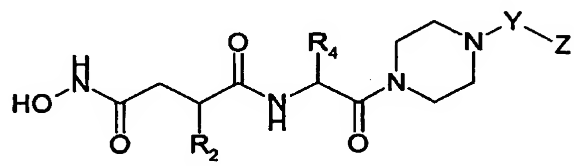
(IID)



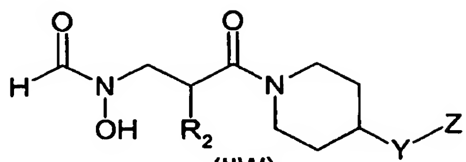
(IIE)



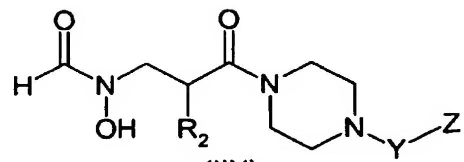
(IIF)



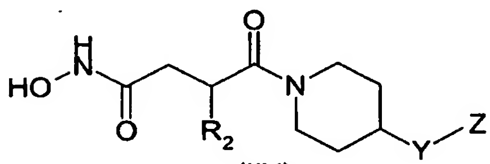
(IIG)



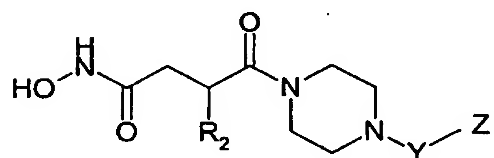
(IIW)



(IIX)



(IIY)



(IIZ)

wherein

R_2 is n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl;

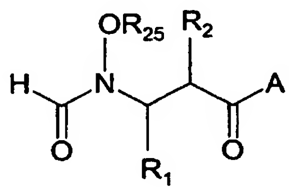
R_4 is tert-butyl, iso-butyl, benzyl or methyl;

Y is $-CH_2-$, -O- or -(C=O)-; and

Z is a phenyl, 3,4-methylenedioxyphenyl, morpholinyl, pyrimidinyl, 1,2,3-thiadiazolyl, 1,4-thiazolyl, benzofuranyl, furanyl, thienyl, pyranyl, pyrrolyl, pyrazolyl, isoxazolyl, or pyridyl ring; in particular, a phenyl, 3,4-methylenedioxyphenyl, morpholinyl, pyrimidin-2-yl, 1,2,3-thiadiazol-5-yl, 1,4-thiazol-5-yl, benzofuran-2-yl, 2-or 3-furanyl, 2- or 3-thienyl, 2- or 3-pyranyl, 2-, 3- or 4-pyrrolyl, 3-, 4- or 5-pyazolyl, 3-, 4- or 5-isoxazolyl, or 2-, 3- or 4-pyridyl ring, which may optionally be substituted as specified in the general description of compounds of the invention.

Particular compounds of the invention, preferred for their potency against organisms which infect the respiratory system, include *N*-[1*S*-(4-benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-2*R*-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide and *N*-[1*S*-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-2*R*-cyclopentylmethyl-*N*-hydroxy-succinamide

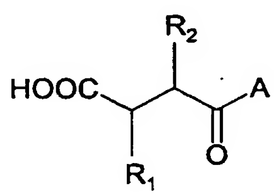
Compounds of the invention in which Q is an N-formylhydroxyamino group may be prepared by deprotecting an O-protected N-formyl-N-hydroxyamino compound of formula (III):



(III)

in which R_1, R_2, and A are as defined in general formula (I) and R_{25} is a hydroxy protecting group removable to leave a hydroxy group by hydrogenolysis or hydrolysis. Benzyl is a preferred R_{25} group for removal by hydrogenolysis, and tert-butyl and tetrahydropyranyl are preferred groups for removal by acid hydrolysis.

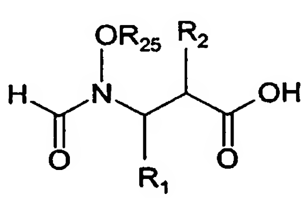
Compounds of the invention in which Q is a hydroxamic acid group may be prepared by reacting the parent compound wherein Q is a carboxylic acid group (IIIA)



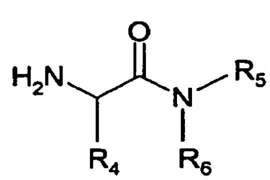
(IIIA)

with hydroxylamine or an N- and/or O-protected hydroxylamine, and thereafter removing any O- or N-protecting groups

Compounds of formula (III) or (IIIA) may be prepared by causing an acid of formula (IV) or (IVC) or an activated derivative thereof to react with an amine of formula (IVA) or (IVB)



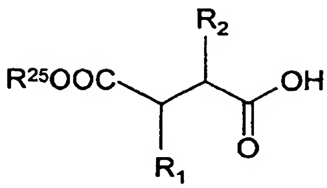
(IV)



(IVA)

HNR_5R_6

(IVB)

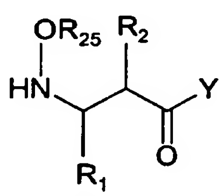


(IVC)

wherein R_1 R_2, R_4, R_5, and R_6 are as defined in general formula (II) except that any substituents in R_1 R_2, R_4, R_5, and R_6 which are potentially reactive in the coupling reaction may themselves be protected from such reaction, and R_{25} is as defined in relation to formula (III) above, and optionally removing protecting groups R_1, R_2, R_4, R_5, and R_6.

Compounds of formula (IVA), (IVB) and (IVC) are prepared by standard literature methods, and many are commercially available.

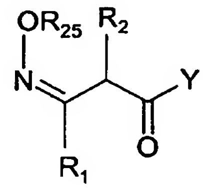
Compounds of formula (IV) may be prepared by N-formylation, for example using acetic anhydride and formic acid, or 1-formylbenzotriazole, of compounds of formula (V)



(V)

wherein R_1, R_2 and R_{25} are as defined in relation to formula (III) and Y is either a chiral auxiliary or an OR_{26} group wherein R_{26} is hydrogen or a hydroxy protecting group. In the case where Y is an OR_{26} group or a chiral auxiliary the hydroxy protecting group or auxiliary is removed after the formylation step to provide the compound of formula (IV). Suitable chiral auxiliaries include substituted oxazolidinones which may be removed by hydrolysis in the presence of base.

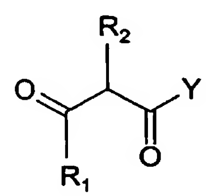
A compound of general formula (V) may be prepared by reduction of an oxime of general formula (VII)



(VII)

wherein R_1, R_2, and R_{25} are as defined above, and Y is either an OR_{26} group as defined above or a chiral auxiliary. Reducing agents include certain metal hydrides (eg sodium cyanoborohydride in acetic acid, triethylsilane or borane/pyridine) and hydrogen in the presence of a suitable catalyst. Following the reduction when the group Y is a chiral auxiliary it may be optionally converted to a OR_{26} group.

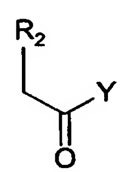
A compound of general formula (VII) can be prepared by reaction of a β-keto carbonyl compound of general formula (VIII)



(VIII)

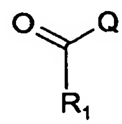
wherein R_1, R_2, and Y are as defined above, with an O-protected hydroxylamine.

β-keto carbonyl compounds (VIII) may be prepared in racemic form by formylation or acylation of a carbonyl compound of general formula (IX)



(IX)

wherein R_2 and Y are as defined above, with a compound of general formula (X)



(X)

wherein R_1 is as defined above and Q is a leaving group such as halogen or alkoxy, in the presence of a base.

The Examples herein provide further details of routes and methods for the preparation of compounds of the invention.

Salts of the compounds of the invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane sulphonates, p-toluenesulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates. Salts may also be formed with bases, for example sodium, potassium, magnesium, and calcium salts.

Compositions with which the invention is concerned may be prepared for administration by any route consistent with the pharmacokinetic properties of the active ingredient(s).

Orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral

liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Safe and effective dosages for different classes of patient and for different disease states will be determined by clinical trial as is required in the art. It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following examples illustrate embodiments of the invention. Note that the "Preparative Example A" does not describe the preparation of a compound of the invention, but is included to provide details of synthetic routes and methods for the preparation of compounds of the invention

^{1}H and ^{13}C NMR spectra were recorded using a Bruker DPX 250 spectrometer at 250.1 and 62.9MHz, respectively. Mass spectra were obtained using a Perkin Elmer Sciex API 165 spectrometer using both positive and negative ionisation modes. Infra-red spectra were recorded on a Perkin Elmer PE 1600 FTIR spectrometer. Analytical HPLC was performed on a Beckman System Gold, using Waters Nova Pak C18 column (150 mm, 3.9 mm) with 20 to 90 % solvent B gradient (1 ml/min) as the mobile phase. [Solvent A: 0.05% TFA in 10% water 90% methanol; Solvent B:

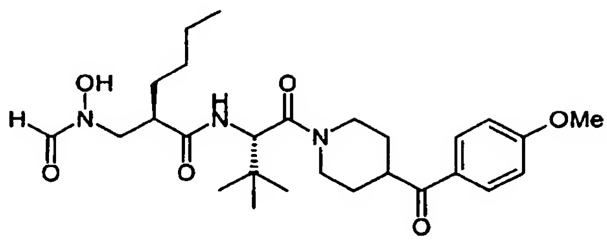
0.05% TFA in 10% methanol 90%], detection wavelength at 230 nm. Preparative HPLC was performed on a Gilson autoprep instrument using a C18 Waters delta prep-pak cartridge (15μm, 300 A, 25 mm, 10 mm) with 20 to 90 % solvent B gradient (6 ml/min) as the mobile phase. [Solvent A water; Solvent B: methanol], UV detection was at 230 nm.

The following abbreviations have been used throughout:

DCM	Dichloromethane
DEAD	Diethyl-azo-dichlorocarboxylate
EDC	N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride
HOAt	1-Hydroxy-7-aza-benzotriazole
HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
LRMS	Low resolution mass spectrometry
NMR	Nuclear magnetic resonance
RT	Retention Time
TLC	Thin layer chromatography
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

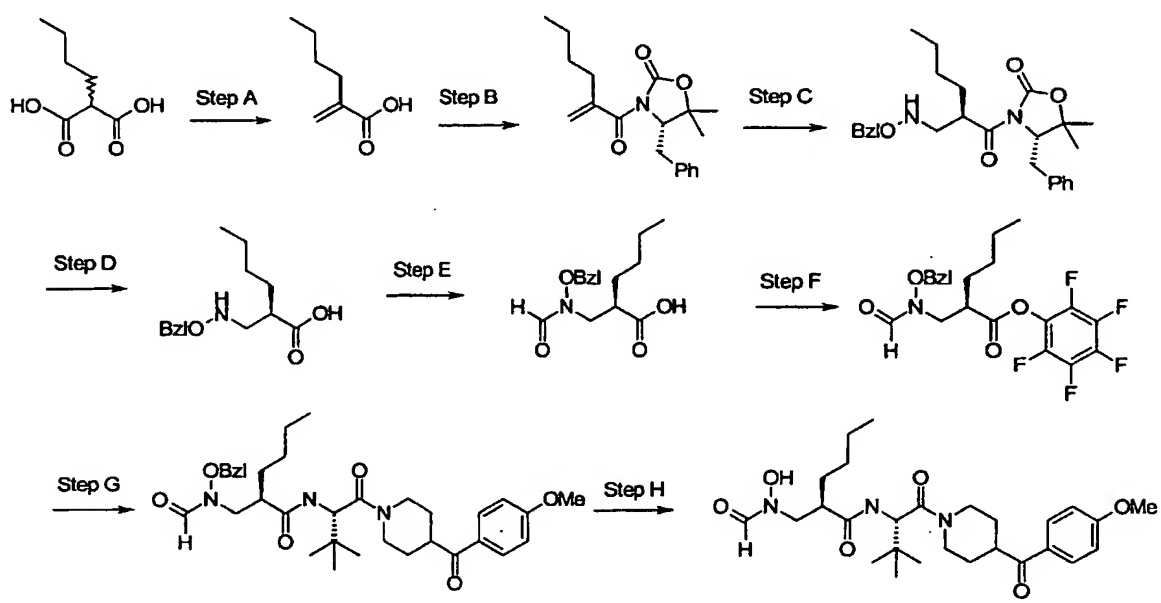
Example 1

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1S-[4-(4-methoxy-benzoyl)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-amide



The title compound was prepared as detailed below (see also Scheme 1)

Scheme 1



Reagents and conditions: A. piperidine, HCHO, EtOH,80°C, O/N; B. ^{t}BuCOCl, Et_3N then 3-lithio-4-benzyl-5,5-dimethyl-oxazolidin-2-one; C. H_2NOBzl, room temp., O/N then pTsOH, EtOAc; D. LiOH, aq. THF, 0°C; E. formic acetic anhydride, Et_3N, THF; F. PfpOH, EDC, HOBt, THF; G. amine, CH_2Cl_2; H. cyclohexene, Pd/C, EtOH.

Step A: 2-Butyl acrylic acid

To a solution of n-butylmalonic acid (17.2 g, 107 mmol) in ethanol (200 ml) was added piperidine (12.76 ml, 129 mmol) and 37% aq. formaldehyde (40.3 ml, 538 mmol). The

solution was heated to 80 °C during which time a precipitate appeared and gradually redissolved over 1 hour. The reaction mixture was stirred at 80 °C overnight then cooled to room temperature. The solvents were removed under reduced pressure and the residue was dissolved in ethyl acetate (200 ml), washed successively with 1 M hydrochloric acid and brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated to give the title compound as a clear oil (13.37 g, 97%). ^{1}H-NMR; δ ($CDCl_3$), 6.29 (1H, s), 5.65 (1H, s), 2.34-2.28 (2H, m), 1.54-1.26 (4H, m), 0.94 (3H, t, J = 7.1 Hz).

Step B: 4S-Benzyl-3-(2-butyl-acryloyl)-5,5-dimethyl-oxazolidin-2-one

2-Butyl acrylic acid (21.5 g, 168 mmol) was dissolved in dry THF (500 ml) and cooled to -78 °C under a blanket of argon. Triethylamine (30 ml, 218 mmol) and pivaloyl chloride (21 ml, 168 mmol) were added at such a rate that the temperature remained below -60 °C. The mixture was stirred at -78 °C for 30 minutes, warmed to room temperature for 2 hours and finally cooled back to -78 °C.

In a separate flask, 4S-benzyl-5,5-dimethyl-oxazolidin-2-one was dissoved in dry THF (500ml) and cooled to -78 °C under a blanket of argon. n-Butyllithium (2.4 M solution in hexanes, 83 ml, 200 mmol) was added slowly and the mixture was stirred for 30 minutes at room temperature. The resulting anion was tranferred *via* a cannula into the original reaction vessel. The mixture was allowed to warm to room temperature and was stirred overnight at room temperature. The reaction was quenched with 1 M potassium hydrogen carbonate (200 ml) and the solvents were removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give an orange oil. TLC analysis revealed the presence of unreacted chiral auxiliary in addition to the required product. A portion of the material (30 g) was dissolved in dichloromethane and flushed through a silica pad to give pure title compound as a yellow oil (25.3 g). ^{1}H-NMR; δ ($CDCl_3$), 7.31-7.19 (5H, m), 5.41 (2H,s), 4.51 (1H, dd, J = 9.7 & 4.2 Hz), 3.32 (1H, dd, J = 14.2 & 4.2 Hz), 2.82

(1H, dd, J = 14.2 & 9.7 Hz), 2.40-2.34 (2H, m), 1.48-1.32 (4H, m), 1.43 (3H, s), 1.27 (3H, s), 0.91 (3H, t, J = 7.1 Hz). Some chiral auxiliary was recovered by flushing the silica pad with methanol.

Step C: 4S-Benzyl-3-[2-(benzyloxyamino-methyl)-hexanoyl]-5,5-dimethyl-oxazolidin-2-one (p-toluenesulfonic acid salt)

4S-Benzyl-3-(2-butyl-acryloyl)-5,5-dimethyl-oxazolidin-2-one (19.8 g, 62.8 mmol) was mixed with O-benzylhydroxylamine (15.4 g, 126 mmol) and stirred overnight at room temperature. The mixture was dissolved in ethyl acetate and the solution was washed with 1 M hydrochloric acid, 1 M sodium carbonate and brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford a pale yellow oil (25.3 g) which was shown by NMR and HPLC analysis to contain 4S-benzyl-3-[2-(benzyloxyamino-methyl)-hexanoyl]-5,5-dimethyl-oxazolidin-2-one (ca. 82% d.e.) along with a trace of starting material. The product was combined with another batch (26.9g, 76% d.e.) and dissolved in ethyl acetate (200 ml). p-Toluenesulfonic acid (22.7 g, 119 mmol) was added and the mixture was cooled to 0 °C. The title compound was obtained as a white crystalline solid by seeding and scratching. Yield: 25.2g, (34%, single diastereoisomer). A second crop (14.7 g, 20%, single diastereoisomer) was also obtained. ^{1}H-NMR;δ ($CDCl_3$), 7.89 (2H, d, J = 8.2 Hz), 7.37-7.12 (10H, m), 7.02 (2H, d, J = 6.9 Hz), 5.28-5.19 (2H, m), 4.55 (1H, m), 4.23 (1H, m), 3.93 (1H, m), 3.58 (1H, m), 2.58 (1H, m), 2.35 (3H, s), 1.67-1.51 (2H, m), 1.29-1.16 (4H, m), 1.25 (3H, s), 1.11 (3H, s), 0.80-0.75 (3H, m).

Step D: 2R-(Benzyloxyamino-methyl)-hexanoic acid

4S-Benzyl-3-[2R-(benzyloxyamino-methyl)-hexanoyl]-5,5-dimethyl-oxazolidin-2-one p-toluenesulfonic acid salt (25.2 g, 40.2 mmol) was partitioned between ethyl acetate and 1 M sodium carbonate. The organic phase was dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residual oil was dissolved in THF (150 ml) and water (50 ml), cooled to 0 °C and treated with lithium hydroxide

(1.86 g, 44.2 mmol). The solution was stirred for 30 minutes at 0 °C, then overnight at room temperature. The reaction was acidified to pH4 with 1 M citric acid and the solvents were removed. The residue was partitioned between dichloromethane and 1 M sodium carbonate. The basic aqueous layer was acidified to pH4 with 1M citric acid and extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated to provide the title compound as a colourless oil (7.4 g, 73%). ^{1}H-NMR;δ ($CDCl_3$), 8.42 (2H, br s), 7.34-7.25 (5H, m), 4.76-4.66 (2H, m), 3.20-3.01 (2H, m), 2.73 (1H, m), 1.70-1.44 (2H, m), 1.34-1.22 (4H, m) and 0.92-0.86 (3H, m).

Step E: 2R-[(Benzyloxy-formylamino)-methyl)]-hexanoic acid

To a solution of 2R-(Benzyloxyamino-methyl)-hexanoic acid (30.6 g, 0.12 mol) in dry THF (300 ml) was added formic acetic anhydride (26.8 ml, 0.31 mol) at 0°C. Triethylamine (18.5 ml, 0.13 mol) was added and the reaction was stirred for 1 h at 0 °C and 60 h at room temperature. The solvent was removed *in vacuo* to yield the title compound as a yellow oil (33.6 g, 99%) which was used in Step F without further purification. ^{1}H-NMR; ($CDCl_3$, rotamers), 8.20-8.08 (0.7H, br s), 8.07-7.92 (0.3H, br s), 7.50-7.25 (5H, br m), 5.07-4.70 (2H, br m), 3.95-3.52 (2H, br m), 2.90-2.66 (1H, br s), 1.72-1.20 (6H, br m), 1.00-0.78 (3H, br s). LRMS: +ve ion 280 [M+1].

Step F: 2R-[(Benzyloxy-formyl-amino)-methyl]-hexanoic acid pentafluoro-phenyl ester

To a solution of 2R-[(Benzyloxy-formylamino)-methyl)]-hexanoic acid (7.8 g, 19.9 mmol) in dry THF (500 ml) was added pentafluorophenol (44.3 g, 0.24 mol), EDC (27.7 g, 0.14 mol) and HOBt (16.2 g, 0.12 mol). The reaction was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate, washed successively with 1 M sodium carbonate (3 x 500 ml) and water (1 x 500 ml), dried over anhydrous magnesium sulfate and filtered. The solvent was removed *in vacuo* to yield a yellow oil (60 g) that was purified by flash chromatography

(5:1, hexane:ethyl acetate → 1:2 hexane:ethyl acetate) to yield a clear oil (42.0 g, 79%). ^{1}H-NMR; δ($CDCl_3$, rotamers), 8.20-8.09 (0.7H, br s), 8.09-7.92 (0.3H, br s), 7.60-7.21 (5H, br m), 5.00-4.70 (2H, br m), 4.04-3.72 (2H, br m), 3.18-3.00 (1H, br s), 1.85-1.57 (2H, br m), 1.50-1.26 (4H, br m), 1.00-0.82 (3H, br m); LRMS: 466 [M+H].

Step G: 2R-[(Benzyloxy-formyl-amino)-methyl]-hexanoic acid {1S-[4-(4-methoxy-benzoyl)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-amide

2R-[(Benzyloxy-formyl-amino)-methyl]-hexanoic acid pentafluorophenyl ester (231mg, 0.52mmol) and 2S-amino-1-[4-(4-methoxy-benzoyl)-piperidin-1-yl]-3,3-dimethyl-butan-1-one (prepared fromr N-benzyloxycarbonyl-L-tert-leucine) (259 mg, 0.78mmol) were dissolved in dichloromethane (6ml) and the mixture was stirred overnight at 27°C. An excess of Amberlyst A-21 ion exchange resin was added and the mixture stirred for 2.5hrs before filtration. The resulting solution was then treated with methyl isocyanate polystyrene resin for 5hrs. The mixture was filtered and solvent was removed under reduced pressure. Mass spectrometric analysis showed presence of pentafluorophenol, so the residue was dissolved in methanol (5ml) and an excess of A-26 carbonate resin was added. The mixture was stirred overnight before filtration and removal of solvent under reduced pressure to afford the title compound as a brown oil (358 mg, 0.60mmol). LRMS: +ve ion 594 [M+H].

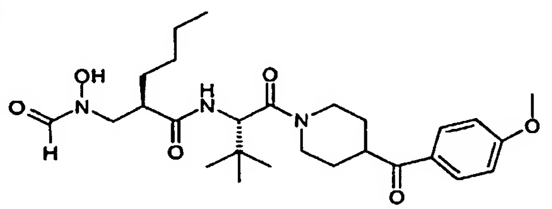
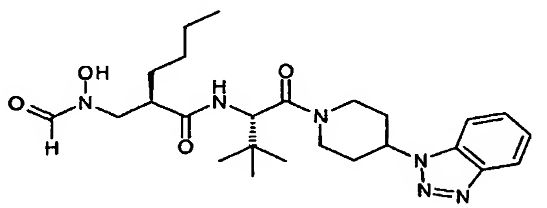
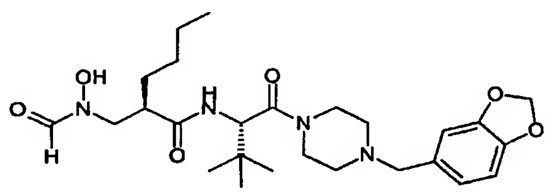
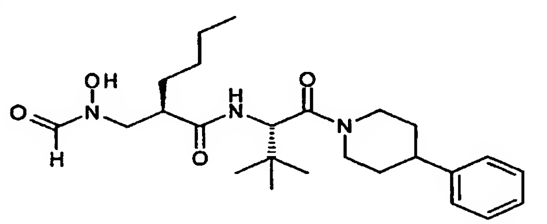
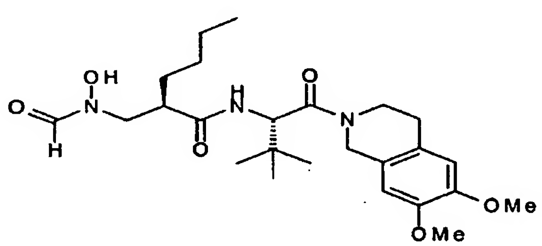
Step H: 2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1S-[4-(4-methoxy-benzoyl)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-amide

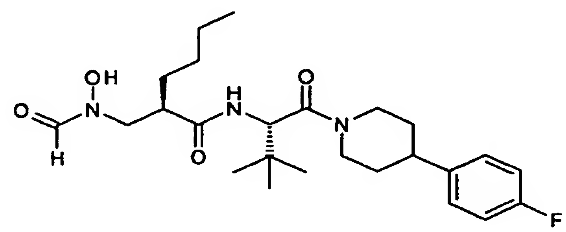
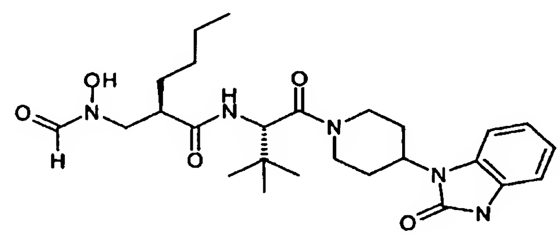
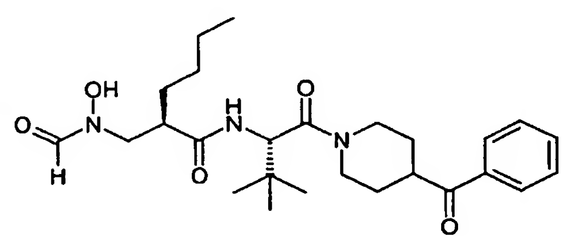
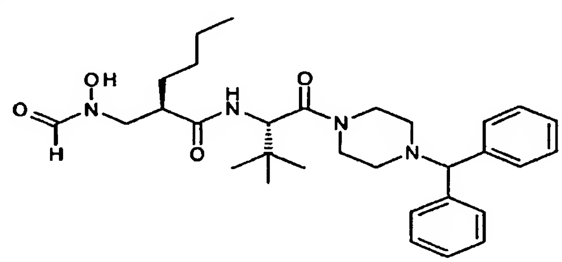
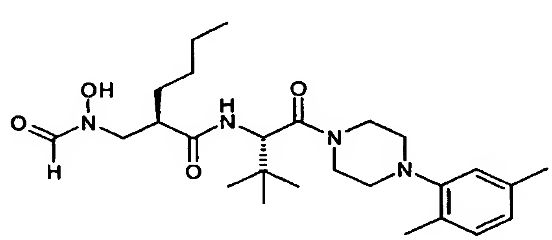
2R-[(Benzyloxy-formyl-amino)-methyl]-hexanoic acid {1S-[4-(4-methoxy-benzoyl)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-amide (358mg, 0.60 mmol) was dissolved in ethanol (6 ml). Cyclohexene (0.60ml) was added and the mixture placed under a blanket of argon. A suspension of 10% palladium on charcoal (40mg) in ethyl acetate (1 ml) was added and the mixture was stirred at 70°C for 5hrs. The reaction mixture was cooled and the catalyst removed by filtration. The filtrate was concentrated to provide the title compound as a brown oil (294mg, 0.58mmol). Characterising data are

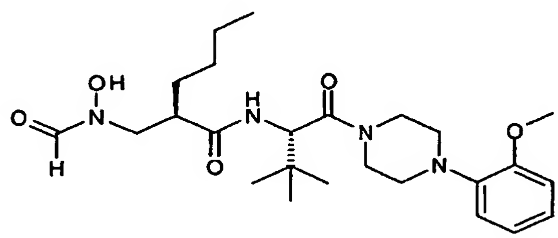
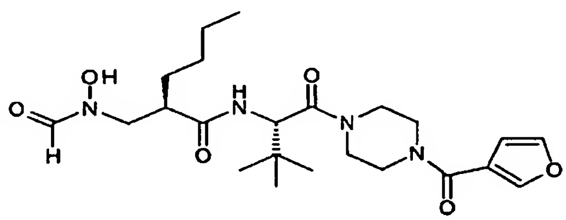
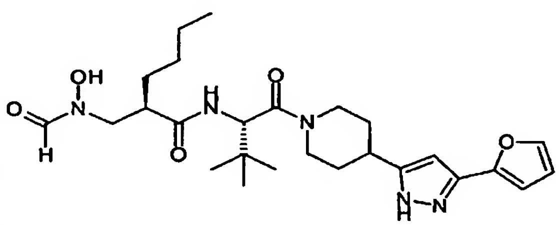
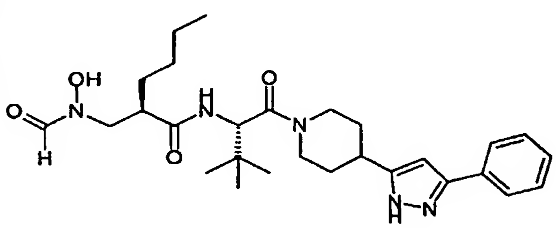
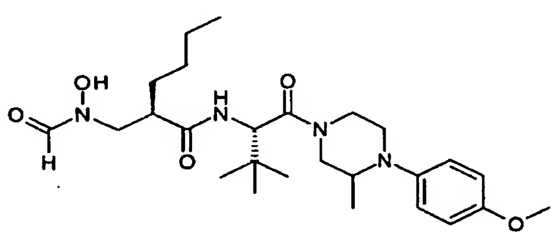
provided in Table 1.

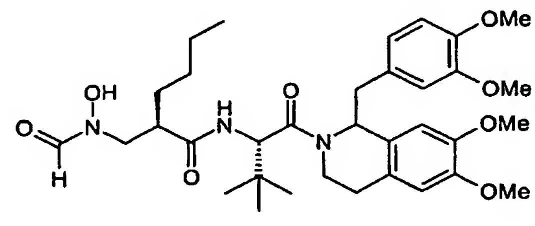
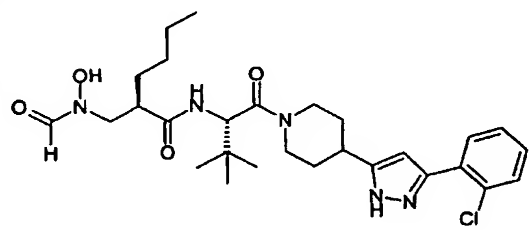
The compounds of Examples 2-13 were prepared by the synthetic route outlined in Scheme 1 and as described in detail for Example 1. Steps G and H were carried out in parallel for all examples. L-*tert*-leucine derivatives were prepared according to established literature methods. Purification of the final compounds, where necessary, was carried out by preparative HPLC.

Table 1

Example	Structure	Mass Spec. Data	HPLC
1		[M+H]=504	RT=21.7mins 88% pure
2		[M+H]=487	RT=20.1mins 85% pure
3		[M+H]=505 [M-H]=503	RT=17.3mins 83% pure
4		[M+H]=447 [M-H]=445	RT=21.5mins 90% pure
5		[M+H]=478 [M+Na]=500 [M-H]=476	RT=20.8mins 95% pure

6		[M+H]=465 [M-H]=463	RT=20.6mins 93% pure
7		[M+H]=502 [M+Na]=524 [M-H]=500	RT=19.3mins 94% pure
8		[M+Na]=496 [M-H]=472	RT=21.2mins 91% pure
9		[M+H]=537 [M-H]=535	RT=19.8mins 95% pure
10		[M+H]=475 [M-H]=473	RT=24.3mins 87% pure

11		[M+H]=477 [M-H]=475	RT=20.3mins 84% pure
12		[M+Na]=487 [M-H]=463	RT=18.7mins 94% pure
13		[M+H]=502	RT=21.0mins 88% pure
14		[M+H]=512 [M-H]=510	RT=21.7mins 84% pure
15		[M+H]=491 [M-H]=489	RT=18.7mins 98% pure

16		[M+Na]=650 [M-H]=626	RT=21.5mins 86% pure
17#		[M+H]=546 [M-H]=544	RT=22.8mins 88% pure

[1]H-NMR; δ (CD_3OD, rotamers), 8.26 (0.4H, s), 7.84 (0.6H, s), 7.69 (2H, m), 7.39 (2H, m), 6.49 (0.4H, s), 6.42 (0.6H, s), 5.01 (0.6H, s), 4.96 (0.4H, s), 4.64 (0.6H, d, J=13.1 Hz), 4.51 (0.4H, d, J=13.2 Hz), 4.36 (0.6H, d, J=13.2 Hz), 4.29 (0.4H, d, J=13.6 Hz), 3.10 (1H, m), 3.43 (0.4H, m), 3.32 (0.6H, m), 3.00 (2H, m), 2.86 (2H, m), 2.09 (2H, m), 1.59 (4H, m), 1.27 (4H, m), 1.02 (9H, m), 0.90 (1.4H, s) and 0.79 (1.6H, s).

The compounds of Examples 18 to 40 were prepared from 2R-[(Benzyloxy-formyl-amino)-methyl]-hexanoic acid pentafluorophenyl ester in a similar way to Example 1 but with the following modifications.

Step G: Generic experimental procedure for the synthesis of an array of amides

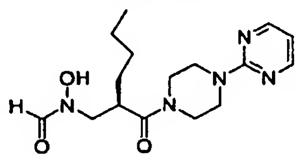
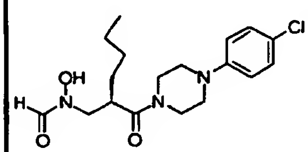
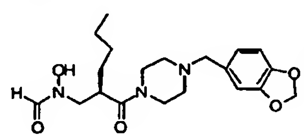
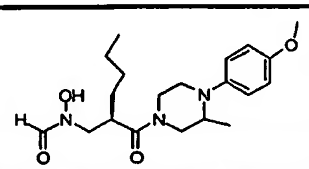
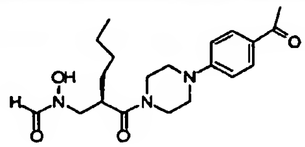
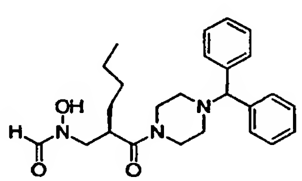
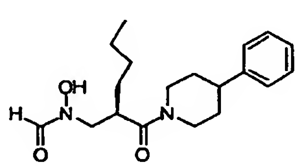
The coupling of amines to the pentafluorophenyl ester were carried out on a Zymate XPII laboratory robot. To a solution of the pentafluorophenyl ester (55.8 mg, 0.12 mmol) in dichoromethane (2 ml) were added the individual amines (0.25 mmol) and the reaction mixtures were stirred at room temperature for 60 h. Purification was effected by removing excess amine and pentafluorophenol using scavenger resins. The pentafluorophenol was removed using a three fold excess (0.36 mmol) of A-26 carbonate resin (3.5 mmol loading). The resin was added to the reaction mixtures and

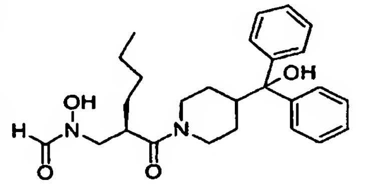
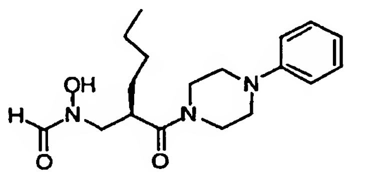
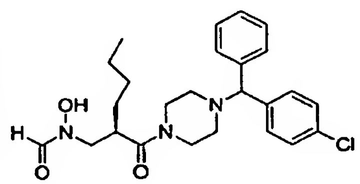
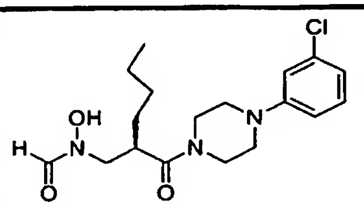
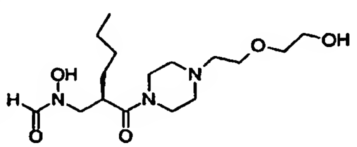
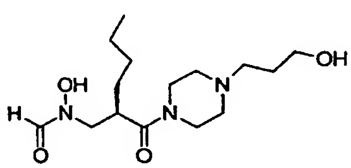
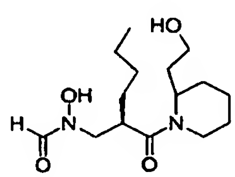
agitated for 24 h, after which time it was filtered off. The excess amines were removed using a three fold excess (0.36 mmol) of methylisocyanate polystyrene resin (1.2 mmol loading). The resin was added to the reaction mixtures and agitated for 4 h, after which time it was filtered off. The solvent was removed *in vacuo* using a Savant Speed Vac Plus to yield the coupled products. Yields were not calculated and the purity and integrity of each compound was verified using HPLC and LRMS.

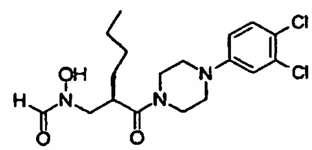
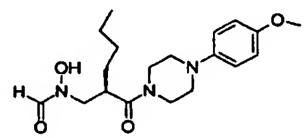
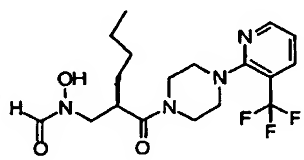
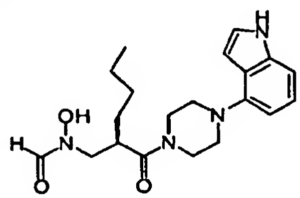
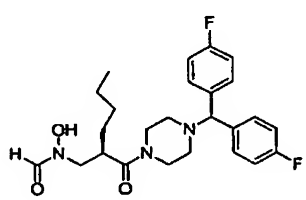
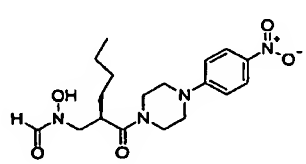
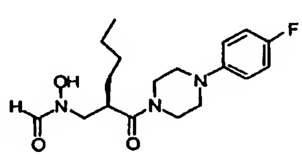
Step H: Generic Transfer Hydrogenation Procedure

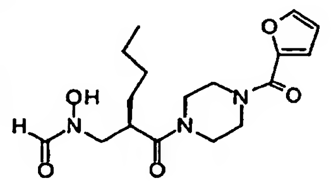
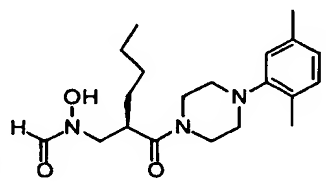
Coupled products from Step G were taken up in an ethanol-cyclohexene solution (3 ml, 10% in cyclohexene) and Pd/C (20% w/w) was added and the reactions stirred at 80 °C for 24 h. The Pd/C was filtered off and the solvent was removed *in vacuo* using a Savant Speed Vac Plus to yield the title compounds (Examples 18 to 40, Table 2). Yields were not calculated and the purity and integrity of each compound was verified using HPLC and LRMS.

Table 2

Example	Structure	Mass Spectral Data	HPLC	Purification
18		336 (M+1, 70)	RT 7.5 min 100%	Ion exchange resin, Prep HPLC
19		368 (M+1, 100)	RT 21.8 min 80%	Resins, Prep HPLC
20		392 (M+1, 100)	RT 8.2 min 100%	Resins Prep HPLC
21		378(M+1, 40) 362([M+1]-Me, 100)	RT 12.0 min and 12.2 min (diastereomers) >98%	Resins Prep HPLC
22		376 (M+1, 100)	RT 18.5 min 100%	Resins
23		424 (M+1, 30), 258 ([M+1]-[C_6H_5]$_2$CH, 100)	RT 17.5 min 95%	Resins
24		333 (M+1, 30)	RT 21.6 min 100%	Resins

25		421 (M+1-H_2O, 50) 437 (M-1, 60)	RT 22.3 min 100%	Resins prep HPLC
26		334 (M+1, 100)	RT 17.7 min 100%	Resins
27		458 (M+1, 20) 258 ([M+1]- [C_6H_5]C_6H_4ClCH, 100)	RT 26.4 min 100%	Resins prep HPLC
28		368 (M+1, 100)	RT 22.1 min 100%	Resins prep HPLC
29		346 (M+1, 100)	2 peaks, RT 3.2 min and 3.6 min 100%	Resins
30		316 (M+1, 100)	2 peaks, RT 3.1 min and 3.5 min 100%	Resins
31		283([M+1]-H_2O, 90)	1 peak with shoulder, RT 16.8 min	Resins

32		402 (M+1, 100)	RT 15.8 min >95%	Resins
33		364 (M+1, 100)	RT 11.7 min >95%	Resins
34		403 (M+1, 100)	RT 14.7 min 95%	Resins
35		373 (M+1, 100)	RT 14.5 min 95%	Resins
36		460 (M+1, 100)	RT 13.3 min >95%	Resins, Prep HPLC
37		379 (M+1, 100),	RT 13.6 min >95%	Resins
38		352 (M+1, 100)	RT 5.9 min > 95%	Resins

39		352 (M+1, 100)	RT 11.3 min >95%	Resins
40		362 (M+1, 100)	15.7 min >95%	Resins

The compounds of the Examples 1-40 are named as follows:

Example 1

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid

51{1S-[4-(4-methoxy-benzoyl)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 2

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid

[1S-(4-benzotriazol-1-yl-piperidine-1-carbonyl)-2,2-dimethyl-propyl]-amide

Example 3

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid

[1S-(4-benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-amide

Example 4

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid

[2,2-dimethyl-1S-(4-phenyl-piperidine-1-carbonyl)-propyl]-amide

Example 5

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid
[1S-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinoline-2-carbonyl)-2,2-dimethyl-propyl]-amide

Example 6

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid
{1S-[4-(4-fluoro-phenyl)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 7

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid
{2,2-dimethyl-1S-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-propyl}-amide

Example 8

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid
[1S-(4-benzoyl-piperidine-1-carbonyl)-2,2-dimethyl-propyl]-amide

Example 9

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid
[1S-(4-benzhydryl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-amide

Example 10

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid
{1S-[4-(2,5-dimethyl-phenyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 11

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid
{1S-[4-(2-methoxy-phenyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 12

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid
{1S-[4-(furan-3-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 13

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid
{1S-[4-(5-furan-2-yl-2*H*-pyrazol-3-yl)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 14

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid
{2,2-dimethyl-1S-[4-(5-phenyl-2*H*-pyrazol-3-yl)-piperidine-1-carbonyl]-propyl}-amide

Example 15

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid
{1S-[4-(4-methoxy-phenyl)-3-methyl-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 16

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid
{1S-[1-(3,4-dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinoline-2-carbonyl]-2,2-dimethyl-propyl}-amide

Example 17

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid
(1S-{4-[5-(2-chloro-phenyl)-2*H*-pyrazol-3-yl]-piperidine-1-carbonyl}-2,2-dimethyl-propyl)-amide

Example 18

N-Hydroxy-N-[2R-(4-pyrimidin-2-yl-piperazine-1-carbonyl)-hexyl]-formamide

Example 19

N-{2R-[4-(4-Chloro-phenyl)-piperazine-1-carbonyl]-hexyl}-N-hydroxy-formamide

Example 20

N-[2R-(4-benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carbonyl)-hexyl]-N-hydroxy-formamide

Example 21

N-Hydroxy-N-{2R-[4-(4-methoxy-phenyl)-3-methyl-piperazine-1-carbonyl]-hexyl}-formamide

Example 22

N-{2R-[4-(4-Acetyl-phenyl)-piperazine-1-carbonyl]-hexyl}-N-hydroxy-formamide

Example 23

N-[2R-(4-Benzhydryl-piperazine-1-carbonyl)-hexyl]-N-hydroxy-formamide

Example 24

N-Hydroxy-N-[2R-(4-phenyl-piperidine-1-carbonyl)-hexyl]-formamide

Example 25

N-Hydroxy-N-{2R-[4-(hydroxy-diphenyl-methyl)-piperidine-1-carbonyl]-hexyl}-formamide

Example 26

N-Hydroxy-N-[2R-(4-phenyl-piperazine-1-carbonyl)-hexyl]-formamide

Example 27

N-(2R-{4-[(4-Chloro-phenyl)-phenyl-methyl]-piperazine-1-carbonyl}-hexyl)-N-hydroxy-formamide

Example 28

N-{2R-[4-(3-Chloro-phenyl)-piperazine-1-carbonyl]-hexyl}-N-hydroxy-formamide

Example 29

N-Hydroxy-N-(2R-{4-[2-(2-hydroxy-ethoxy)-ethyl]-piperazine-1-carbonyl}-hexyl)-formamide

Example 30

N-Hydroxy-N-{2R-[4-(3-hydroxy-propyl)-piperazine-1-carbonyl]-hexyl}-formamide

Example 31

N-Hydroxy-N-{2R-[2-(2-hydroxy-ethyl)-piperazine-1-carbonyl]-hexyl}-formamide

Example 32

N-{2R-[4-(3,4-Dichloro-phenyl)-piperazine-1-carbonyl]-hexyl}-N-hydroxy-formamide

Example 33

N-Hydroxy-N-{2R-[4-(4-methoxy-phenyl)-piperazine-1-carbonyl]-hexyl}-formamide

Example 34

N-Hydroxy-N-{2R-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazine-1-carbonyl]-hexyl}-formamide

Example 35

N-Hydroxy-N-{2R-[4-(1H-indol-7-yl)-piperazine-1-carbonyl]-hexyl}-formamide

Example 36

N-(2R-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazine-1-carbonyl}-hexyl)-N-hydroxy-formamide

Example 37

N-Hydroxy-N-{2R-[4-(4-nitro-phenyl)-piperazine-1-carbonyl]-hexyl}-formamide

Example 38

N-{2R-[4-(4-Fluoro-phenyl)-piperazine-1-carbonyl]-hexyl}-N-hydroxy-formamide

Example 39

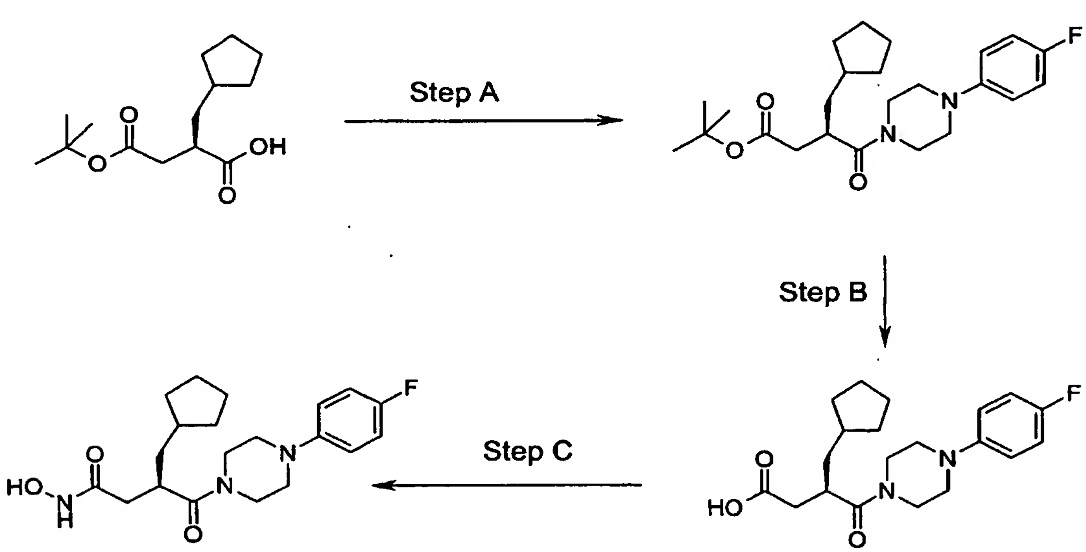
N-{2R-[4-(Furan-2-carbonyl)-piperazine-1-carbonyl]-hexyl}-N-hydroxy-formamide

Example 40

N-{2R-[4-(2,5-Dimethyl-phenyl)-piperazine-1-carbonyl]-hexyl}-N-hydroxy-formamide

The compounds of Examples 41 and 42 below were prepared in solution by parallel synthesis. The general synthetic route (Scheme B) is outlined in detail below for Example 41. 2R-Cyclopentylmethyl-succinic acid 4-*tert*-butyl ester was prepared by analogy with methods in patent application number WO 92/13831

Scheme B



Reagents and conditions: Step A, Amine, PyBOP, HOAt, DIPEA, CH_2Cl_2;
Step B: TFA, CH_2Cl_2; Step C: NH_2OH, NMM, DMF, PyBOP, HOAt, Et_3N, CH_2Cl_2

Example 41

The preparation of 3R-Cyclopentylmethyl-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-N-hydroxy-4-oxo-butyramide

Step A: 3R-Cyclopentylmethyl-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-4-oxo-butyric acid *tert*-butyl ester

To a solution of 2R-Cyclopentylmethyl-succinic acid 4-*tert*-butyl ester **1** (250 mg, 1.0 mmol) in dichloromethane (5 ml) was added PyBOP (670 mg, 1.3 mmol), HOAt (145 mg, 1.0 mmol), DIPEA (278 μl, 1.7 mmol) and amine (211 mg, 1.2 mmol), the reaction mixture was stirred at room temperature for 24 h. The solvent was removed *in vacuo* to yield an orange oil (800 mg), which was taken up in ethyl acetate (50 ml) and was washed with 1M sodium carbonate (2 x 50 ml), water (1 x 50 ml) and dried over anhydrous magnesium sulphate. The solvent was removed *in vacuo* to yield the title compound as a yellow oil (600 mg), which was purified by preparative HPLC.

Step B: 3R-Cyclopentylmethyl-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-4-oxo-butyric acid

To a solution of 3R-Cyclopentylmethyl-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-4-oxo-butyric acid *tert*-butyl ester in dichloromethane (3 ml) was added TFA (2 ml) at 0°C, the reaction mixture was stirred at 0°C for 0.5 h and at room temperature for 1.5 h, after which time no starting material remained. The solvent was removed *in vacuo* and the TFA was azeotroped with toluene to yield the title compound as an orange oil (364 mg), which was progressed to the next step without further purification.

Step C: 3R-Cyclopentylmethyl-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-N-hydroxy-4-oxo-butyramide

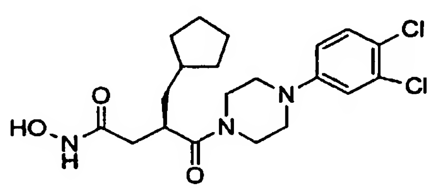
To a solution of 3R-Cyclopentylmethyl-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-4-oxo-butyric acid (364 mg, 1.0 mmol) in dichloromethane (3 ml) was added PyBOP (575 mg,

1.1 mmol), HOAt (14 mg, 0.1 mmol), and Et_3N (279 µl, 2.0 mmol). To a solution of hydroxylamine hydrochloride (105 mg, 1.5 mmol) in a separate flask in DMF (2 ml) was added NMM (161 µl, 1.5 mmol). This solution was then added to the solution of acid and the reaction mixture was stirred at RT for 60 h. The solvent was removed *in vacuo* and the resulting residue was taken up in dichloromethane (5 ml) and was washed with 1M sodium carbonate (1 x 5 ml), water (1 x 5 ml) dried over anhydrous magnesium sulphate and the solvent removed *in vacuo* to yield a yellow oil (520 mg). The product was purified by prep HPLC. LRMS –ve ion: 376 (M-1, 80%), P; +ve ion 345 ([M+1]-32, 40%), P-NHOH; HPLC data: RT 5.6 min 97%

The following compound was prepared in a manner identical to that of Example 41 starting with 2R-Cyclopentylmethyl-succinic acid 4-*tert*-butyl ester and 3,4-dichloro-phenyl-piperazine.

Example 42

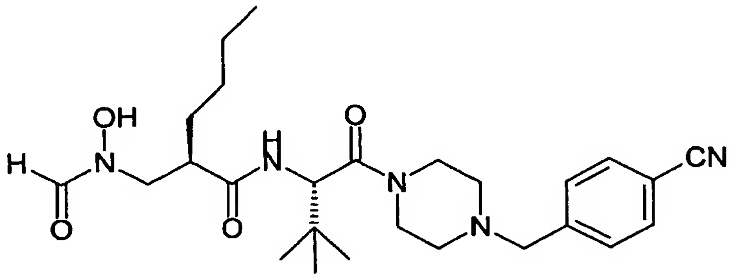
3R-Cyclopentylmethyl-4-[4-(3,4-dichloro-phenyl)-piperazin-1-yl]-N-hydroxy-4-oxo-butyramide



The title compound was purified by preparative HPLC. LRMS –ve ion: 326 (M-1, 40%); +ve ion: 395 ([M+1]-32, 40%), P-NHOH; HPLC data: RT 6.4 min, 98%.

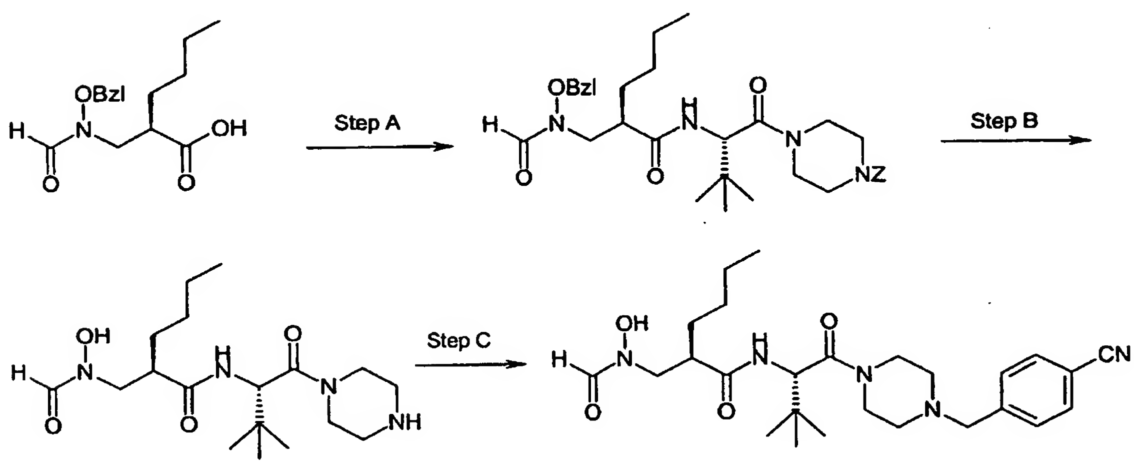
Example 43

2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(4-cyano-benzyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide



The title compound was prepared as detailed below (see Scheme 2) from 2*R*-[(Benzoyloxy-formylamino)-methyl]-hexanoic acid (see Scheme 1).

Scheme 2



Reagents and conditions: A. EDC, HOAt, DMF, amine. B. Pd/C, EtOH, H_2(g). C.Et_3N, DCM, *p*-nitrile benzyl bromide.

Step A: 2*R*-[(Benzyloxy-formyl-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(2-phenoxy-acetyl)-piperazine-1-carbonyl]-propyl}-amide

To a solution of 2R-[(Benzoyloxy-formylamino)-methyl]-hexanoic acid (7.0g, 25 mmols) in DMF was added EDC (5.3 g, 27.5 mmol), 4-(2S-Amino-3,3-dimethyl-butyryl)-piperazine-1-carboxylic acid benzyl ester (10.0 g, 30 mmol) and HOAt (0.34g, 2.5 mmol). The reaction was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate, washed successively with 1M hydrochloric acid, 1M sodium carbonate and saturated sodium chloride solution, dried over anhydrous magnesium sulfate and filtered. The solvent was removed *in vacuo* to yield a yellow oil (9.6 g) that was purified by flash chromatography (3% methanol/DCM) to yield a white foam (6.7g, 45%). ^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.13 (0.6H, s), 7.89 (0.4H, s), 7.36 (10H, m), 6.26 (1H, d, J = 9.2 Hz), 5.15 (2H, s), 4.88 (2H, m), 4.82 (1H, d, J = 9.3 Hz), 3.56 (10H, m), 2.54 (1H, m), 1.25 (6H, m), 0.94 (9H, s), 0.83 (3H, t, J = 6.9 Hz). LRMS: +ve ion 617 [M+Na].

Step B: 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2,2-dimethyl-1*S*-(piperazine-1-carbonyl)-propyl]-amide

To a solution of 2*R*-[(Benzyloxy-formyl-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(2-phenoxy-acetyl)-piperazine-1-carbonyl]-propyl}-amide (6.5 g, 11 mmol) in ethanol (100 ml), under a blanket of argon, was added a suspension of 10% palladium on charcoal (670 mg) in ethyl acetate (15 ml). Hydrogen was bubbled through the suspension for 30 minutes and then the reaction was stirred under an atmosphere of hydrogen for 3 hours 45 minutes. The palladium catalyst was filtered off and the solvent removed *in vacuo* to yield a white foam (4.28 g. 100%). ^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.39 (0.3H, s), 7.80 (0.7H, s), 6.82 (1H, m), 4.90 (1H, m), 3.87 (3H, m), 3.50 (3H, m), 2.80 (5H, m), 1.39 (6H, m), 0.99 (3H, s), 0.95 (6H, s), 0.87 (3H, t, J = 6.7 Hz). LRMS +ve ion 397 [M+1], 419 [M+Na], -ve ion 395 [M-1].

Step C: 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(4-cyano-benzyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

To a stirred solution of 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2,2-dimethyl-1*S*-(piperazine-1-carbonyl)-propyl]-amide in dichloromethane (4 ml) was added triethylamine (85 µl, 0.6 mmol) and *p*-nitrile benzyl bromide (110 mg, 0.56 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* to yield a yellow oil that was purified by preparative HPLC to obtain a white foam (108 mg, 44%) Characterisation data is provided in Table 2.

The compounds of Examples 44-48 were prepared by the synthetic route outlined in Scheme 2 and as described in detail for Example 43. Step C was carried out in parallel for all examples. Characterisation data for the compounds is provided in Table 2. Examples 49-54 were prepared from 2*R*-[(Benzyloxy-formyl-amino)-methyl]-3-cyclopentyl-propionic acid in a similar manner. Characterisation data for the compounds is provided in Table 3. L-*tert*-leucine derivatives were prepared according to established literature methods. Purification of the final compounds, where necessary, was carried out by preparative HPLC.

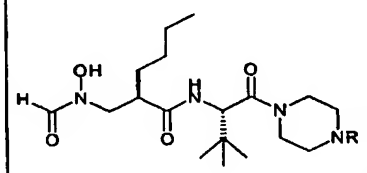
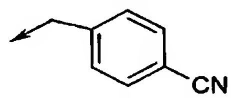
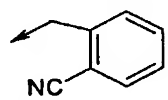
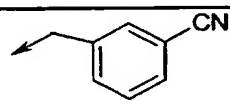
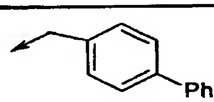
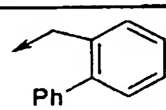
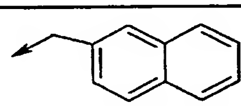
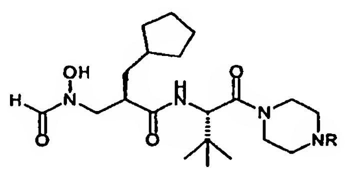
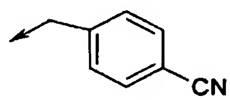
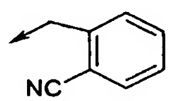
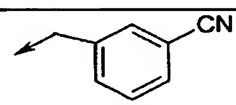
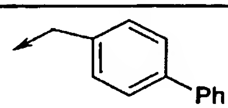
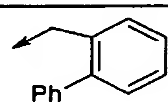
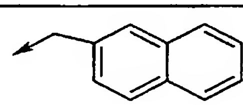
Table 2				
Example	R =	LCMS ions seen	LCMS Retention time (min)	LCMS Purity (%)
43		M+1=486 M+Na=508	2.6	>90
44		M+1=486 M+Na=508	2.65	>90
45		M+1=486 M+Na=508	2.6	>90
46		M+1=537 M+Na=559	3.65	>90
47		M+1=537 M+Na=559	3.58	>90
48		M+1=511 M+Na=533	3.38	>90

Table 3				
Example	R =	LCMS ions seen	LCMS Retention time (mins)	LCMS Purity (%)
49		M+1=512 M+Na=534	2.97	>90
50		M+1=512 M+Na=534	3.02	>90
51		M+1=512 M+Na=534	2.95	>90
52		M+1=563	3.88	>90
53		M+1=563 M+Na=585	3.83	>90
54		M+1=537 M+Na=559	3.63	>90

The compounds of examples 44-54 are named as follows:

Example 44. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(2-cyano-benzyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 45. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(3-cyano-benzyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 46. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [1*S*-(4-biphenyl-4-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-amide

Example 47. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [1*S*-(4-biphenyl-2-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-amide

Example 48. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2,2-dimethyl-1*S*-(4-naphthalen-2-ylmethyl-piperazine-1-carbonyl)-propyl]-amide

Example 49. N-{1*S*-[4-(4-Cyano-benzyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-2*R*-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide

Example 50. N-{1*S*-[4-(2-Cyano-benzyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-2*R*-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide

Example 51. N-{1*S*-[4-(3-Cyano-benzyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-2*S*-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide

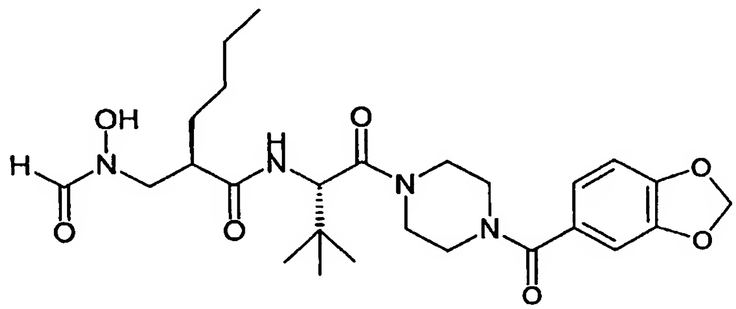
Example 52. N-[1*S*-(4-Biphenyl-4-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-2*R*-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide

Example 53. N-[1*S*-(4-Biphenyl-2-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-2*R*-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide

Example 54. 2*R*-Cyclopentylmethyl-N-[2,2-dimethyl-1*S*-(4-naphthalen-2-ylmethyl-piperazine-1-carbonyl)-propyl]-3-(formyl-hydroxy-amino)-propionamide

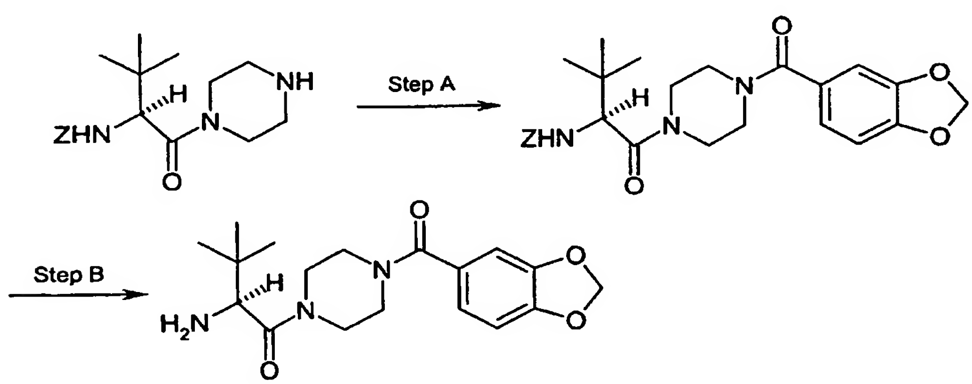
Example 55

2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(3a,7a-dihydro-benzo[1,3]dioxole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide



Example 55 was prepared from 2*R*-[(Benzoyloxy-formylamino)-methyl]-hexanoic acid by analogy with methods described in Scheme 1. 2-Amino-1*S*-[4-(3a,7a-dihydro-benzo[1,3]dioxole-5-carbonyl)-piperazin-1-yl]-3,3-dimethyl-butan-1-one was prepared as detailed below (Scheme 3).

Scheme 3



Reagents and conditions: A. Et_3N, 3,4 methylenedioxybenzoyl chloride, CH_2Cl_2

B. Pd/C, EtOH, H_2(g).

Step A: {1*S*-[4-(3a,7a-Dihydro-benzo[1,3]dioxole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid benzyl ester

To a solution of [2,2-Dimethyl-1*S*-(piperazine-1-carbonyl)-propyl]-carbamic acid benzyl ester (3.2 g, 9.6 mmol) in anhydrous dichloromethane (50 ml) under an atmosphere of argon, was added triethylamine (2.8 ml, 20 mmol) and 3,4 methylenedioxybenzoyl chloride (2.0 g, 10.8 mmol). The reaction was stirred overnight at room temperature. The reaction mixture was diluted with dichloromethane, washed successively with 1M hydrochloric acid, 1M sodium carbonate and saturated sodium chloride solution, dried over anhydrous magnesium sulfate and filtered. The solvent was removed *in vacuo* to yield a yellow oil which was purified by flash chromatography (5% methanol/ dichloromethane) to obtain a white foam (3.5 g, 76%). LRMS: +ve ion 504 [M+Na], ^{1}H-NMR; δ ($CDCl_3$), 7.35 (5H, s), 6.93 (2H, m), 6.84 (1H, m), 6.01 (2H, s), 5.55 (1H, d, J = 9.5 Hz), 5.06 (2H, m), 4.54 (1H, d, J = 9.7 Hz), 3.65 (8H, m), 0.99 (9H, s).

Step B: 2-Amino-1*S*-[4-(3a,7a-dihydro-benzo[1,3]dioxole-5-carbonyl)-piperazin-1-yl]-3,3-dimethyl-butan-1-one

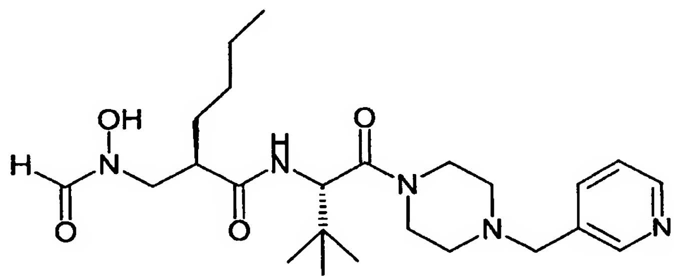
To a solution of {1*S*-[4-(3a,7a-Dihydro-benzo[1,3]dioxole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid benzyl ester (3.5 g, 7.3 mmol) in ethanol (70 ml), under a blanket of argon, was added 10% palladium on charcoal (350 mg). Hydrogen was bubbled through the suspension for 1 hour and then the reaction was stirred under an atmosphere of hydrogen for 2 hours. The palladium catalyst was filtered off and the solvent removed *in vacuo* to yield a white foam (2.5 g. 99%). LRMS: +ve ion 348 [M+1], 370 [M+Na], ^{1}H-NMR; δ ($CDCl_3$), 6.94 (2H, m), 6.84 (1H, m), 6.01 (2H, s), 3.64 (9H, m), 1.61 (2H, s), 0.98 (9H, s).

The following example 56 was prepared in a similar way to Example 55 except 3,4

methylenedioxybenzoyl chloride was replaced with 3-(bromomethyl) pyridine.

Example 56

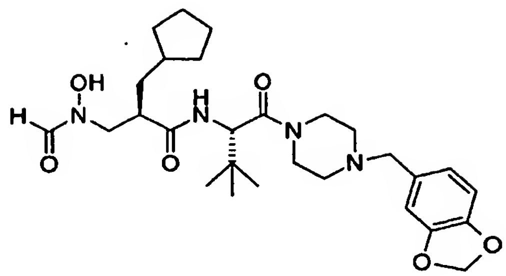
2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2,2-dimethyl-1*S*-(4-pyridin-3-ylmethyl-piperazine-1-carbonyl)-propyl]-amide



^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.62 (2H, m), 8.39 (0.4H, s), 7.82 (0.6H, s), 7.67 (1H, d, J=7.7Hz), 7.28 (1H, m), 6.92 (0.4H, m), 6.76 (0.6H, m), 4.91 (1H, m), 4.02 (0.4H, m), 3.82 (3H, m), 3.51 (4.6H, m), 2.84 (0.6H, m), 2.68 (0.4H, m), 2.36 (4H, m), 1.53 (2H, m), 1.25 (4H, m), 0.97 (3H, s), 0.93 (6H, s), 0.88 (3H, t, J = 7.0 Hz). ^{13}C-NMR; δ (CDCl3), 175.5, 173.3, 170.3, 170.2, 150.6, 149.1, 147.2, 133.6, 123.9, 66.2, 60.3, 54.8, 54.5, 53.7, 53.5, 53.4, 53.3, 53.1, 52.9, 52.8, 52.5, 48.9, 47.3, 47.1, 46.1, 45.1, 2.5 and 42.4. LRMS: +ve ion 484 [M+Na].

Example 57

_N_-[1*S*-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-2*R*-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide



The title compound was prepared as detailed in scheme 1 from 2*S*-Amino-1-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-3,3-dimethyl-butan-1-one (see scheme 3, piperonyl piperazine is commerically available) and 2*R*-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionic acid pentafluorophenyl ester.

^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.40 (0.4H, bs), 7.82 (0.6H, bs), 6.83 (1H, bs), 6.76-6.63 (2H, m), 6.58-6.54 (1H, m), 5.94 (2H, s), 4.87 (1H, m), 4.10-3.28 (9H, m), 2.87-2.16 (7H, m), 1.85-1.33 (10H, m); 1.09 (1H, m); 0.98 (3.6H, m); 0.93 (5.4H, m); LRMS: +ve ion 531 [M+H], 553 [M+Na]. -ve ion 529 [M-1]; HPLC: RT=4.91 min, 97% pure.

Examples 58-67 were prepared by synthetic methods analogous to those described for Example 55, using the relevant acid chloride or carboxylic acid in Step A of Scheme 3. The compounds were synthesised in parallel and purification of the final compounds, where necessary, was carried out by preparative HPLC. Characterisation data for these compounds are provided in Table 4.

Examples 68-79 were prepared by synthetic methods analogous to those described for Example 43, but using an acid chloride, carboxylic acid or sulfonyl chloride in place of the bromide in Step C of Scheme 2. Purification of the final compounds, where necessary, was carried out by preparative HPLC. Characterisation data for these compounds are provided in Table 5.

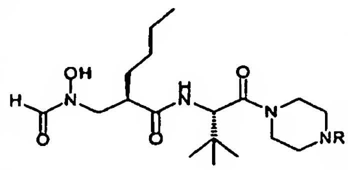
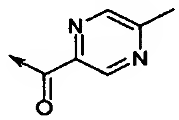
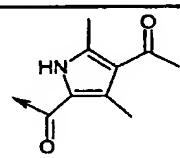
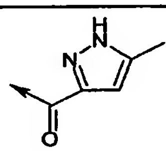
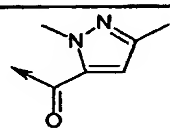
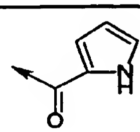
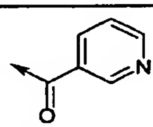
Table 4				
Example	R =	Mass Spec.	HPLC Retention time	HPLC Purity (%)
58		M+Na=513	4.9	>84
59		M+Na=556	5.1	>87
60		M+Na=501	4.8	>84
61		M+Na=515	5	>85
62		M+Na=486	5.1	>83
63		M+Na=498	3.8	>95

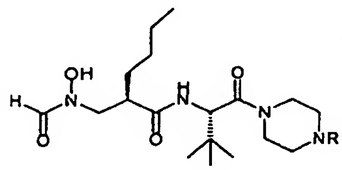
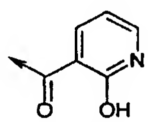
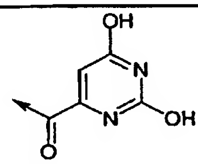
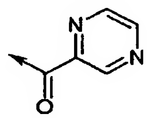
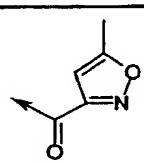
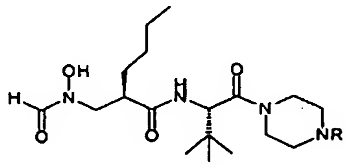
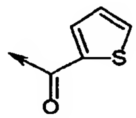
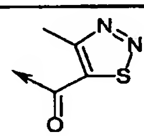
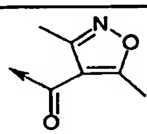
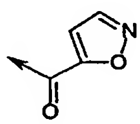
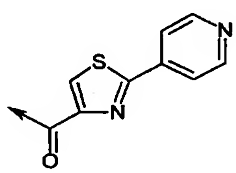
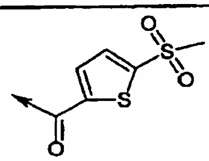
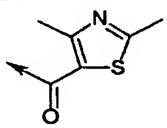
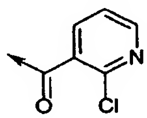
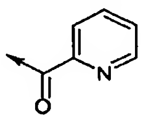
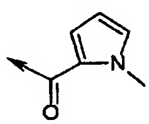
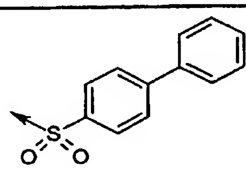
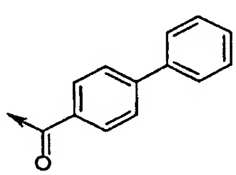
Table 4				
Example	R =	Mass Spec.	HPLC Retention time	HPLC Purity (%)
64		M+Na=514	4.4	98
65		M+Na=531	4.5	93
66		M+Na=499	7.8	>96
67		M+Na=502 M-1=478	10.4	92

Table 5				
Example	R =	Mass Spec.	HPLC Retention time	HPLC Purity (%)
68		M+Na=503 M-1=479	4.9	100
69		M+Na=519 M-1=495	4.9	100
70		M+Na=516 M-1=492	4.7	96
71		M+Na=488 M-1=464	4.6	99
72		M+1=559 M+Na=581 M-1=557	4.5	>88

Example	R =	Mass Spec.	HPLC Retention time	HPLC Purity (%)
73		M+1=559 M+Na=581 M-1=557	5.2	100
74		M+1=510 M+Na=532 M-1=508	5	>95
75		M+Na=532	4.96	99
76		M+1=476 M+Na=498 M-1=474	4.77	95
77		M+1=478 M+Na=500 M-1=476	5.09	100
78		M+1=587 M+Na=609 M-1=585	6.08	100
79		M+1=551 M+Na=573 M-1=549	6.01	97

The compounds of Examples 58 - 79 are named as follows:

Example 58. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(5-methyl-pyrazine-2-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 59. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(4-acetyl-3,5-dimethyl-H-pyrrole-2-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 60. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(5-methyl-1H-pyrazole-3-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 61. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(2,5-dimethyl-2-H-pyrazole-3-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 62. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(1-H-pyrrole-2-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 63. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(pyridine-3-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 64. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(2-hydroxy-pyridine-3-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 65. 2*R*[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(2,6-dihydroxy-pyrimidine-4-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 66. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(pyrazine-2-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 67. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(5-methyl-isoxazole-3-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 68. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(thiophene-2-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 69. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(4-methyl-[1,2,3]thiadiazole-5-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 70. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(3,5-dimethyl-isoxazole-4-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 71. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(isoxazole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 72. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(2-pyridin-4-yl-thiazole-4-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 73. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(5-methanesulfonyl-thiophene-2-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 74. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(2,4-dimethyl-thiazole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 75. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(2-chloro-pyridine-3-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 76. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(pyridine-2-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

Example 77. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {2,2-dimethyl-1*S*-[4-(1-methyl-1-H-pyrrole-2-carbonyl)-piperazine-1-carbonyl]-propyl}-amide

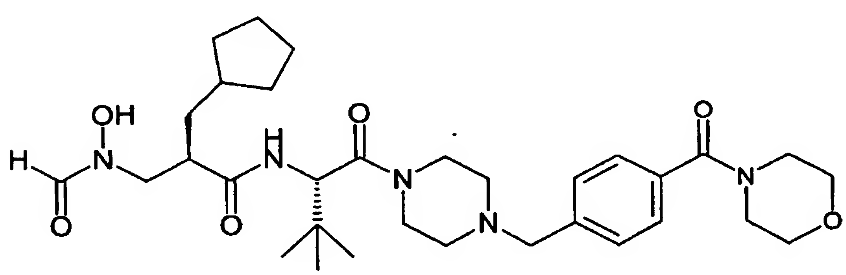
Example 78. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(biphenyl-4-sulfonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Example 79. 2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(biphenyl-4-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide

Examples 80 and 81 were prepared in a similar manner to Example 43 from 2R-[(Benzyloxy-formyl-amino)-methyl]-3-cyclopentyl-propionic acid.

Example 80

2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid (2,2-dimethyl-1*S*-{4-[4-(morpholine-4-carbonyl)-benzyl]-piperazine-1-carbonyl}-propyl)-amide

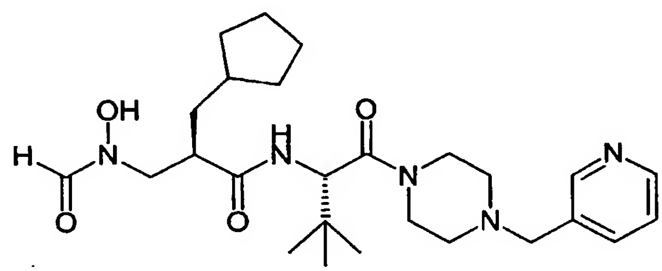


[1]H-NMR; δ ($CDCl_3$, rotamers), 8.38 (0.4 H, s), 7.81 (0.6H, s), 7.36 (4H, s), 6.77 (0.4H, d, J=8.9Hz), 6.62 (0.6H, d, J=9.3Hz), 4.88 (1H, m), 4.03 (0.4H, dd, J=14.6, 7.1Hz), 3.91 (1H, m), 3.76 (8H, m), 3.51 (5.6H, m), 3.38 (1H, m), 2.84 (0.6H, m), 2.69 (0.4H, m), 2.55 (2H, m), 2.30 (2H, m), 1.57 (9H, m), 1.05 (2H, m), 0.98 (3H, s), 0.94 (6H, s). [13]C-NMR; δ ($CDCl_3$, rotamers), 176.0, 173.3, 170.7, 170.1, 156.5,

140.2, 134.8, 129.5, 127.7, 67.3, 62.8, 55.0, 54.5, 53.8, 53.6, 53.2, 53.1, 52.2, 49.0, 47.4, 47.2, 46.0, 44.9, 42.7, 42.4, 38.5, 38.2, 36.9, 36.7, 35.9, 33.2, 27.0, 25.6 and 25.5. LRMS: +ve ion 600 [M+H], 622 [M+Na]. HPLC: RT=4.63 min, 100% pure.

Example 81

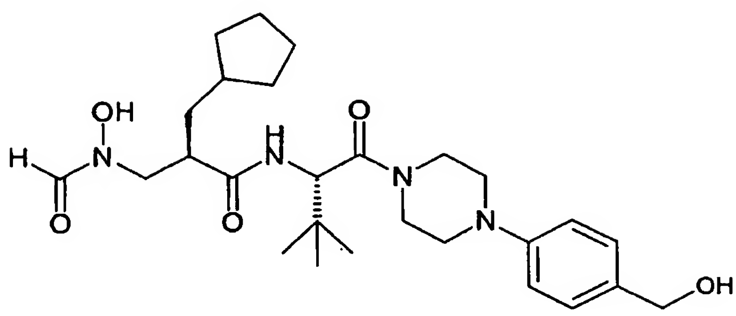
2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2,2-dimethyl-1*S*-(4-pyridin-3-ylmethyl-piperazine-1-carbonyl)-propyl]-amide



^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.53 (2 H, m), 8.40 (0.3H, s), 7.81 (0.7H, s), 7.65 (1H, d, J=7.7Hz), 7.27 (1H, m), 6.76 (0.3H, d, J=8.8Hz), 6.67 (0.7H, d, J=8.9Hz), 4.89 (1H, m), 4.03 (0.3H, m), 3.92 (1H, m0, 3.77 (1.7H, m) 3.47 (5H, m), 2.86 (0.7H, m), 2.69 (0.3H, m), 2.56 (2H, m0, 2.31 (2H, m), 1.64 (9H, m), 1.07 (2H, m), 0.98 (3H, s), 0.93 (6H, s). ^{13}C-NMR; δ ($CDCl_3$, rotamers), 175.5, 173.0, 169.8, 150.3, 148.8, 136.7, 133.1, 123.4, 60.0, 54.6, 54.1, 53.4, 53.2, 52.8, 52.7, 52.1, 48.7, 46.9, 46.8, 45.6, 44.5, 42.2, 42.0, 38.2, 37.9, 36.5, 36.3, 5.6, 32.8, 32.7, 6.7, 25.3 and 25.2. LRMS: +ve ion 488 [M+H], 510 [M+Na]. HPLC: RT=4.48 min, 98% pure.

Example 82

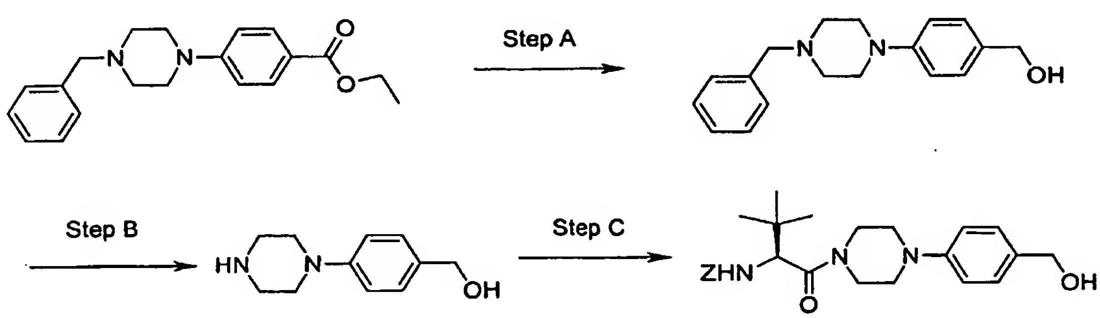
2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid {1*S*-[4-(4-hydroxymethyl-phenyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-amide



LRMS: +ve ion 485 [M-OH]$^+$, -ve ion 501 [M-H]. HPLC RT=5.8 min, 95% pure.

The title compound was prepared from 3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionic acid pentafluoro-phenyl ester and 4-(4-Benzyl-piperazin-1-yl)-benzoic acid ethyl ester which is a known literature compound. {1-[4-(4-Hydroxymethyl-phenyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid benzyl ester (Scheme 4) was deprotected and coupled to the pentafluorophenyl ester in a manner identical to that in Scheme 1.

Scheme 4



Reagents and conditions: A. $LiAlH_4$, THF, 75℃; B. Pd/C, EtOH, H_2 (g); C. EDC, HOAt, Et_3N, CH_2Cl_2.

Step A [4-(4-Benzyl-piperazin-1-yl)-phenyl]-methanol

To a solution of lithium aluminium hydride (88 mg, 2.3 mmol) in dry THF (20 ml) was

added 4-(4-Benzyl-piperazin-1-yl)-benzoic acid ethyl ester (500 mg, 1.5 mmol). The suspension was stirred at 75 °C for 4 h. The reaction mixture was allowed to cool and a few drops of water were added followed by 1-2 drops of 1M sodium hydroxide. A white precipitate formed and was filtered off, the THF was removed *in vacuo*, and brine (10 ml) was added to the residue. This mixture was washed with ether (2 x 50 ml, the ether layers were combined and dried over anhydrous magnesium sulphate and the solvent removed *in vacuo* to yield a yellow solid (405 mg). Flash chromatography (3%MeOH/CH_2Cl_2) allowed the isolation of the title compound as a white solid (331 mg, 76%). ^{1}H-NMR δ ($CDCl_3$) 7.38-7.21 (7H, m, ArH), 6.91-6.85 (2H, m, ArH), 4.59 (2H, s), 3.57 (2H, s), 3.21-3.17 (4H, m), 2.61-2.58 (4H, m). HPLC: 2.4 min (99% @ 214 nm); LRMS +ve: 283 (M+1, 80).

Step B: (4-Piperazin-1-yl-phenyl)-methanol

To a solution of [4-(4-Benzyl-piperazin-1-yl)-phenyl]-methanol in EtOH (50 ml) under a blanket of argon was added a suspension of 10% palladium on charcoal (1.5 g) in EtOH (150 ml). Hydrogen was bubbled through the suspension for 1 h and then the reaction mixture was stirred under a blanket of hydrogen for 60 h at RT. The catalyst was filtered off and the solvent removed *in vacuo* to yield the title compound as a white solid (4.8 g, 100%). ^{1}H-NMR δ ($CDCl_3$) 7.30-7.21 (2H, m, ArH), 6.94-6.88 (2H, m, ArH), 4.59 (2H, s), 3.18-2.98 (8H, m). HPLC: 0.5 min (37% @ 214 nm), 0.7 min (55% @ 214 nm), multiple peaks due to salt formation from TFA buffer; LRMS +ve: 193 (M+1, 70).

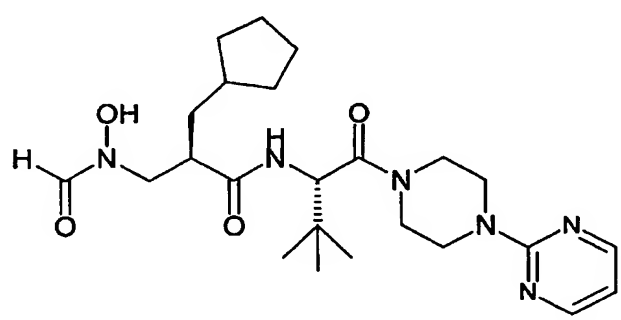
Step C: {1-[4-(4-Hydroxymethyl-phenyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid benzyl ester

To a solution of CBz protected *tert*-leucine (7.4 g, 28 mmol) in dichloromethane (20 ml) was added (4-Piperazin-1-yl-phenyl)-methanol in a solution of DMF/ dichloromethane (50:50, 250 ml). EDC (7.3 g, 38 mmol), HOAt (0.34g, 2.5 mmol) and triethylamine (7.0 ml, 50 mmol) were subsequently added. The reaction mixture

was stirred at RT for 18 h. The solvent was removed *in vacuo* to yield a yellow oil, which was taken up in dichloromethane (300 ml) and was washed with 1M sodium carbonate (2 x 200 ml), 1M hydrochloric acid (1 x 200 ml), brine (1 x 200ml) dried (anhydrous magnesium sulphate) and the solvent removed *in vacuo* to yield a white foam (11.8 g). Flash chromatography 2% MeOH/dichloromethane allowed the isolation of the title compound as a white foam (7.01 g, 63%). HPLC 5.7 min (100% @ 214 nm). LRMS +ve 462 (M+Na, 60), 440 (M+1, 20), 422 (M-OH, 100).

Example 83

2*R*-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2,2-dimethyl-1*S*-(4-pyrimidin-2-yl-piperazine-1-carbonyl)-propyl]-amide

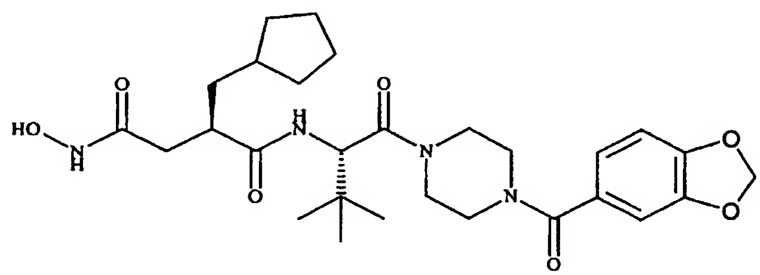


Prepared by method analogous to Example 82.

^{1}H-NMR; δ ($CDCl_3$), 8.40 (0.3H, s), 8.33 (2H, d, J=4.8Hz), 7.82 (0.7H, s), 6.76 (1H, d, J=8.4Hz), 6.55 (1H, t, J=4.7Hz), 4.94 (1H, m), 4.09-3.37 (10H, m), 2.86-2.78 (0.7H, m), 2.72-2.65 (0.3H, m,) 1.63-1.18 (6H, m), 1.02 (3H, s), 0.97 (6H, s), 0.85 (3H, m). ^{13}C-NMR; δ ($CDCl_3$), 176.0, 173.3, 170.5, 161.9, 158.2, 111.1, 55.3, 54.7, 52.1, 48.7, 47.1, 47.0, 46.5, 45.1, 44.3, 44.2, 44.0, 43.9, 42.6, 42.4, 35.9, 30.3, 30.2, 29.7, 29.6, 27.1, 22.9 and 14.3. LRMS: +ve ion 449 [M+H], 471 [M+Na], -ve ion 447 [M-H]. HPLC: RT=4.99 min, 100% pure.

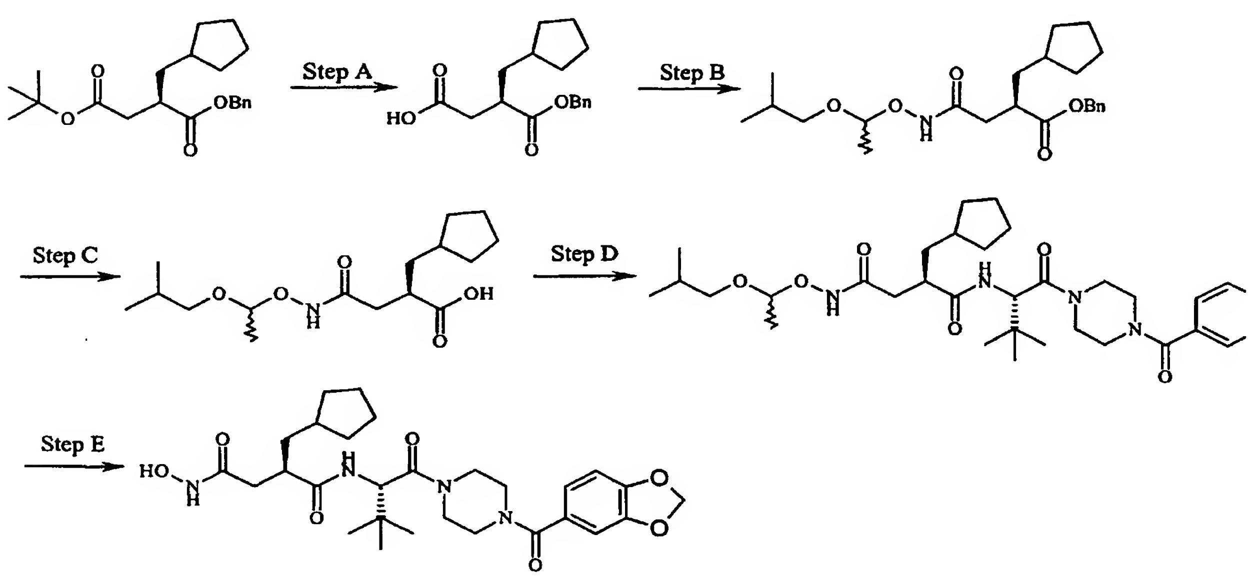
Example 84

***N*[1]-{1*S*-[4-(Benzo[1,3]dioxole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-2*R*-cyclopentylmethyl-*N*[4]-hydroxy-succinamide**



Example 84 was prepared as detailed below (see Scheme 5) from 2*R*-Cyclopentylmethyl-succinic acid 4-*tert*-butyl ester, prepared by analogous methods described in patent WO 92/13831, and 2-Amino-1*S*-[4-(benzo[1,3]dioxole-5-carbonyl)-piperazin-1-yl]-3,3-dimethyl-butan-1-one, prepared by methods described in Scheme 3.

Scheme 5



Reagents and conditions: A. TFA, CH_2Cl_2; B. EDC, DMF, HOAt, hydroxylamine. C. Pd/C, EtOH, $H_{2\,(g)}$. D. EDC, DMF. E. MeOH, 1M HCl.

Step A: 2*R*-Cyclopentylmethyl-succinic acid 1-benzyl ester

To a solution of 2*R*-Cyclopentylmethyl-succinic acid 4-*tert*-butyl ester (960 mg, 2.7 mmol) in dichloromethane (30 ml), was added TFA (30 ml). The reaction mixture was left at –4 °C for 18h. The solvent was removed *in vacuo* and the TFA co-evaporated with toluene and ether *in vacuo* to yield a yellow oil (810 mg, 100%).
^{1}H-NMR δ ($CDCl_3$), 7.38-7.29 (5H, m), 5.15 (2H, s), 2.93-2.87 (1H, m), 2.78 (1H, dd, J_1=9.485 J_2=16.81), 2.52 (1H, dd, J_1=4.92 J_2=17.01), 1.84-1.63 (3H, m), 1.62-1.53 (2H, m), 1.52-1.40 (3H, m), 1.09-1.02 (2H, m).

Step B: 2*R*-Cyclopentylmethyl-*N*-(1-isobutoxy-ethoxy)-succinamic acid benzyl ester

To a solution of 2*R*-Cyclopentylmethyl-succinic acid 1-benzyl ester (810 mg, 2.8 mmol) in DMF, was added EDC (805 mg, 4.2 mmol), HOAt, (10% w/w) and O-(1-Isobutoxy-ethyl)-hydroxylamine (745 mg, 5.6 mmol). The reaction was left stirring for 60 h at room temperature. The solvent was removed *in vacuo*, the residue was taken up in ethyl acetate and washed successively with 1M hydrochloric acid, 1M sodium carbonate and saturated sodium chloride solution. The organic phase was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield a yellow oil (1.07g, 97%).
^{1}H NMR; δ ($CDCl_3$), 8.05 (1H, bs), 7.34-7.27 (5H, m), 5.17:5.10 (2H, AB q, J=12.36), 4.92-4.88 (1H, m), 3.52 (1H, dd, J_1=6.643 J_2=9.340), 3.271 (1H, dd, J_1=6.734 J_2=9.267), 3.06-2.95 (1H, m), 2.52-2.23 (2H, m), 1.89-1.41 (11H, m), 1.36 (3H, dd, J_1=3.53 J_2=5.303), 1.06 (2H, bs), 0.919 (6H, d, 6.63).
ESMS; +ve ion 428 [M+Na]

Step C: 2*R*-Cyclopentylmethyl-*N*-(1-isobutoxy-ethoxy)-succinamic acid

To a solution of 2*R*-Cyclopentylmethyl-*N*-(1-isobutoxy-ethoxy)-succinamic acid benzyl ester (925 mg, 2.3 mmol) in ethanol, under a blanket of argon, was added palladium on charcoal (10% w/w). Hydrogen was bubbled through the suspension for 30 minutes and the reaction stirred under an atmosphere of hydrogen for 3 hours. The palladium catalyst was filtered off and the solvent removed *in vacuo* to yield a yellow oil (720 mg, 100%).

^{1}H-NMR; δ ($CDCl_3$), 4.93 (1H, m), 3.559 (1H, dd, J_1= 6.620 J_2= 9.292), 3.292 (1H, dd, J_1= 6.70 J_2= 9.330), 2.94 (1H, m), 2.49-2.29 (2H, m), 1.93-1.75 (5H, m), 1.61-1.44 (6H, m), 1.377 (3H, dd, J_1= 1.237 J_2= 5.237), 1.08 (2H, m), 0.919 (6H, d, J_1= 6.65).
ESMS; +ve ion 338 [M+Na], -ve ion 314 [M-1]

Step D: *N*^{1}-{1*S*-[4-(Benzo[1,3]dioxole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-2*R*-cyclopentylmethyl-*N*^{4}-(1-isobutoxy-ethoxy)-succinamide

To a solution of 2*R*-Cyclopentylmethyl-*N*-(1-isobutoxy-ethoxy)-succinamic acid (150 mg, 0.48 mmol) in DMF (7.5 ml), was added 2-Amino-1*S*-[4-(benzo[1,3]dioxole-5-carbonyl)-piperazin-1-yl]-3,3-dimethyl-butan-1-one (165 mg, 0.5 mmol) and stirred for 5 minutes. EDC (96 mg, 0.5 mmol) was added and the reaction mixture stirred at room temperature over the weekend. The solvent was removed *in vacuo* and the residue taken up in ethyl acetate and washed successively with 1M hydrochloric acid, 1M sodium carbonate and saturated sodium chloride solution. The organic phase was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield an 'off white' solid (227mg, 74%).

^{1}H-NMR; δ ($CDCl_3$), 6.87 (2H, m), 6.01 (2H, s), 4.873 (1H, m), 3.94-3.67 (4H, m), 3.64-3.23 (10H, m), 2.773 (1H, m), 2.43-2.19 (2H, m), 1.89-1.39 (14H, m), 1.357 (3H, dd, J_1= 2.350 J_2=5.306), 1.117 (2H, m), 0.987 (9H, s), 0.913 (6H, d,

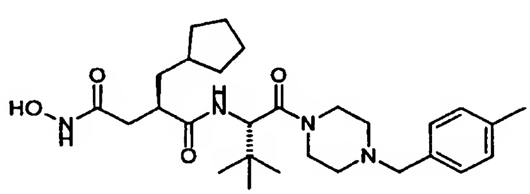
J_1=6.66).ESMS; +ve ion 667 [M+Na]

Step E: *N*[1]-{1*S*-[4-(Benzo[1,3]dioxole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-2*R*-cyclopentylmethyl-*N*[4]-hydroxy-succinamide

N[1]-{1*S*-[4-(Benzo[1,3]dioxole-5-carbonyl)-piperazine-1-carbonyl]-2,2-dimethyl-propyl}-2*R*-cyclopentylmethyl-*N*[4]-(1-isobutoxy-ethoxy)-succinamide(198 mg, 0.31 mmol) was dissolved in a 50/50 mixture of methanol and 1M hydrochloric acid (16 ml) and stirred at room temperature for 30 minutes. Pre-washed Amberlyst resin 95 was added until pH 7 was reached and was then filtered under suction and washed with methanol. The filtrate was concentrated *in vacuo* with ethanol to yield a yellowish solid that was purified by preparative HPLC to yield the title compound as a white foam (62 mg). ^{1}H-NMR; δ (MeOD), 6.935 (1H, s), 6.926 (2H, dd, J_1= 7.854 J_2= 34.375), 6.018 (2H, s), 4.863 (1H, s), 3.902-3.384 (8H, m), 2.893 (1H, m), 2.323 (1H, dd, J_1=7.86 J_2=14.31), 2.193 (1H, dd, J_1=6.23 J_2=14.39), 1.824 (1H, m), 1.645 (5H, m), 1.491 (2H, m), 1.374 (1H, m), 1.033 (11H, m); ^{13}C-NMR; δ (MeOD), 177.7, 172.8, 172.2, 171.0, 151.3, 149.7, 130.2, 123.3, 109.7, 103.5, 56.5, 48.1, 43.6, 43.4, 40.1, 39.8, 37.4, 36.4, 34.0, 27.5, 26.5; ESMS; +ve ion 567 [M+Na], -ve ion 543 [M-1]

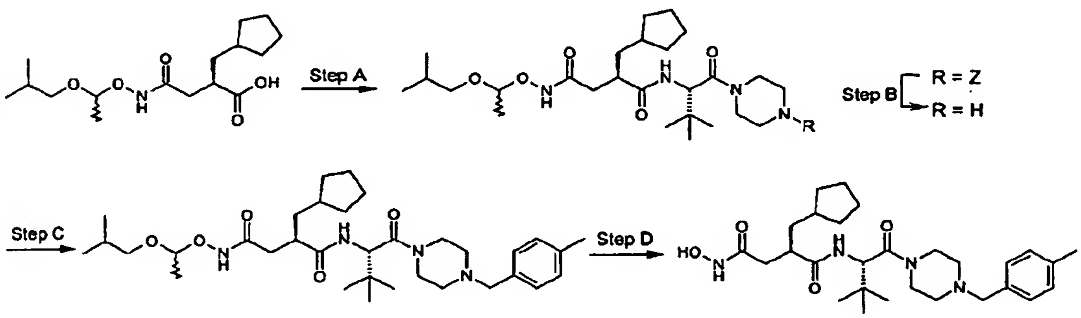
Preparative Example A

2*R*-Cyclopentylmethyl-*N*[1]-{2,2-dimethyl-1*S*-[4-(4-methyl-benzyl)-piperazine-1-carbonyl]-propyl}-*N*[4]-hydroxy-succinamide



The title compound was prepared as detailed below (see scheme 6) from 2-Cyclopentylmethyl-*N*-(1-isobutoxy-ethoxy)-succinamic acid (scheme 5).

Scheme 6



Reagents and conditions: A. 4-(2-Amino-3,3-dimethyl-butyryl)-piperazine-1-carboxylic acid benzyl ester, WSC, NEt_3, CH_2Cl_2; B. Pd/C, H_2, MeOH; C. 4-methyl benzyl bromide, NEt_3, CH_2Cl_2; D. HCl 1N, MeOH.

Step A: 4-{2*S*-[2*R*-Cyclopentylmethyl-3-(1-isobutoxy-ethoxycarbamoyl)-propionylamino]-3,3-dimethyl-butyryl}-piperazine-1-carboxylic acid benzyl ester

To a cold (0°C) solution of the acid (6.8 g, 16.1 mmol) in dichloromethane (80 ml), the hydrochloride salt of the amine (8.65 g, 19.4 mmol) was added followed by triethylamine (2.92 ml, 21 mmol) and then WSC (3.72 g, 19.4 mmol). The reaction mixture was stirred overnight allowing the temperature to come back to room temperature. The reaction mixture was then diluted with dichloromethane and washed with water (80 ml), with Na_2CO_3 and brine. The combined organic layer was dried over $MgSO_4$ and the solvent was removed in *vacuo* to yield a yellowish foam which was purified through flash chromatography to give a 100% pure compound (8 g, 79% yield).

^{1}H-NMR; δ ($CDCl_3$), 8.20 (1H,m), 7.32 (5H, m), 6.45 (1H, m), 5.11 (2H, s), 4.91-4.82 (2H, m), 3.87-3.21 (12H, m), 2.41 (1H, m), 2.73 (1H, m), 1.90-1.40 (14H, m), 1.36 (3H, m), 0.98 (9H, s), 0.90 (6H, d)

Step B: 2*R*-Cyclopentylmethyl-*N*[1]-[2,2-dimethyl-1*S*-(piperazine-1-carbonyl)-propyl]-*N*[4]-(1-isobutoxy-ethoxy)-succinamide

To a suspension of the Z-protected piperazine (8 g, 12.7 mmol) in MeOH (100 ml) was added Pd/C (0.8 g) and then H_2 was bubbled for 1h. The reaction mixture was then stirred under a blanket of H_2 for another hour. Pd/C was filtered off through a celite pad to give the desired compound in a 99% yield.
ESMS; +ve ion 498 [M+1], -ve ion 496 [M-1]; HPLC: RT = 5.21 min

Step C: 2*R*-Cyclopentylmethyl-*N*[1]-{2,2-dimethyl-1*S*-[4-(4-methyl-benzyl)-piperazine-1-carbonyl]-propyl}-*N*[4]-(1-isobutoxy-ethoxy)-succinamide

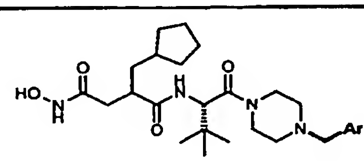
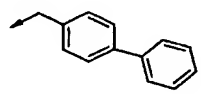
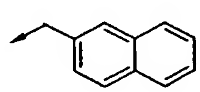
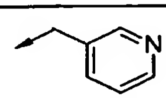
To a solution of 4-methyl benzyl bromide (74 mg, 0.4 mmol) in dichloromethane (2 ml) were added a solution of the piperazine in dichloromethane (1.2 ml, 0.33 mmol) and Net_3 (60 ml, 0.4 mmol). The reaction mixture was stirred at room temperature for 12 hours. Water was added (1.5 ml) and the resulting solution filtered through polypropylene hydrophobic cartridges (1PS filter). The solvent was then removed under reduced pressure to afford the expected adduct.

Step D: 2*R*-Cyclopentylmethyl-*N*[1]-{2,2-dimethyl-1*S*-[4-(4-methyl-benzyl)-piperazine-1-carbonyl]-propyl}-*N*[4]-hydroxy-succinamide

To a solution of the latter in MeOH (4 ml) was added HCl 1N (600 ml) and the reaction mixture was stirred for 2 h. Then 60 ml of NEt_3 were added and the solvent was removed under reduced pressure. The crude reaction mixture was purified through HPLC.

The compounds of Examples 85-87 were prepared by the synthetic route outlined in Scheme 5 and as described in detail for Preparative Example A. Step C and Step D were carried out in parallel format for all examples. Characterisation data for the

compounds are provided in Table 6.

Table 6			
Example	**Structures**	**Mass Spec**	**Retention Time (min)**
85		M+1=563 M-1=561	5.2
86		M+1=537 M-1=535	5.03
87		M+1=488 M-1=486	4.17

The compounds of Examples 85 - 87 are named as follows:

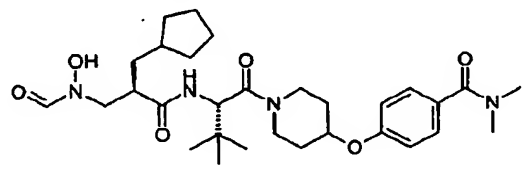
Example 85. N^1-[1*S*-(4-Biphenyl-4-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-2*R*-cyclopentylmethyl-N^4-hydroxy-succinamide

Example 86. 2*R*-Cyclopentylmethyl-N^1-[2,2-dimethyl-1*S*-(4-naphthalen-2-ylmethyl-piperazine-1-carbonyl)-propyl]-N^4-hydroxy-succinamide

Example 87. 2*R*-Cyclopentylmethyl-N^1-[2,2-dimethyl-1*S*-(4-pyridin-3-ylmethyl-piperazine-1-carbonyl)-propyl]-N^4-hydroxy-succinamide

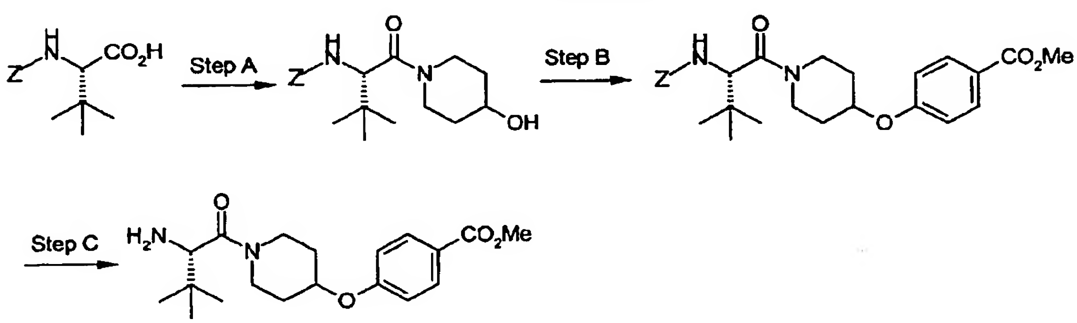
Example 88

4-(1-{2S-[3-(Benzyloxy-formyl-amino)-2R-cyclopentylmethyl-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-N,N-dimethyl benzamide



The title compound was prepared as detailed below (see scheme 8) from the the 3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionic acid pentafluorophenyl ester and 4-[1-(2*S*-Benzyloxycarbonylamino-3,3-dimethyl-butyryl)-piperidin-4-yloxy]-benzoic acid methyl ester (see scheme 7).

Scheme 7



Reagents and conditions: Step A: 4-hydroxy piperidine,WSC, HOAt, CH_2Cl_2; Step B: 4-hydroxy methyl benzoate, DEAD, PPh_3, THF; Step C: H_2, Pd/C, EtOH, reflux

Step A: [1S-(4-Hydroxy-piperidine-1-carbonyl)-2,2-dimethyl-propyl]-carbamic acid benzyl ester

To a cold solution (0°C) of the Z-*tert*-leucine (3.48 g, 13.1 mmol) and 4-hydroxy piperidine (1.4 g, 13.7 mmol) in CH_2Cl_2 (40 ml) were added WSC (2.75 g, 14.4 g) followed by HOAt (18 mg, 0.13 mmol). The reaction mixture was stirred at room

temperature for 12 hours and then washed with water and brine. The combined organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to furnish a yellow oil which was purified through flash chromatography. The desired compound was obtained in 64% yield.

^1H NMR; δ ($CDCl_3$), 7.34 (5H, s), 5.58 (1H, m), 5.08 (2H, m), 4.60 (1H, m), 3.91 (3H, m), 3.49-3.05 (2H, m), 1.91 (4H, m), 0.98 (9H, d, J=3.57); ESMS; +ve ion 371 [M+Na]; HPLC: RT = 5.44 min.

Step B: 4-[1-(2*S*-Benzyloxycarbonylamino-3,3-dimethyl-butyryl)-piperidin-4-yloxy]-benzoic acid methyl ester

To a cold solution (0°C) of the latter compound (1.45 g, 4.2 mmol), 4-hydroxy methyl benzoate (0.7 g, 4.6 mmol) and triphenylphosphine (1.48 g, 5.46 mmol) were added dropwise followed by the addition of DEAD (0.86 ml, 5.46 mmol). The reaction mixture was stirred at 0°C for 2.5 hours. Thf was removed in *vacuo* and the crude residue was taken-up in ethyl acetate. The organic layer was washed with water and brine and subsequently dried over $MgSO_4$. After purification through flash chromatography the expected compound was obtained as a pure white foam in 70% yield.

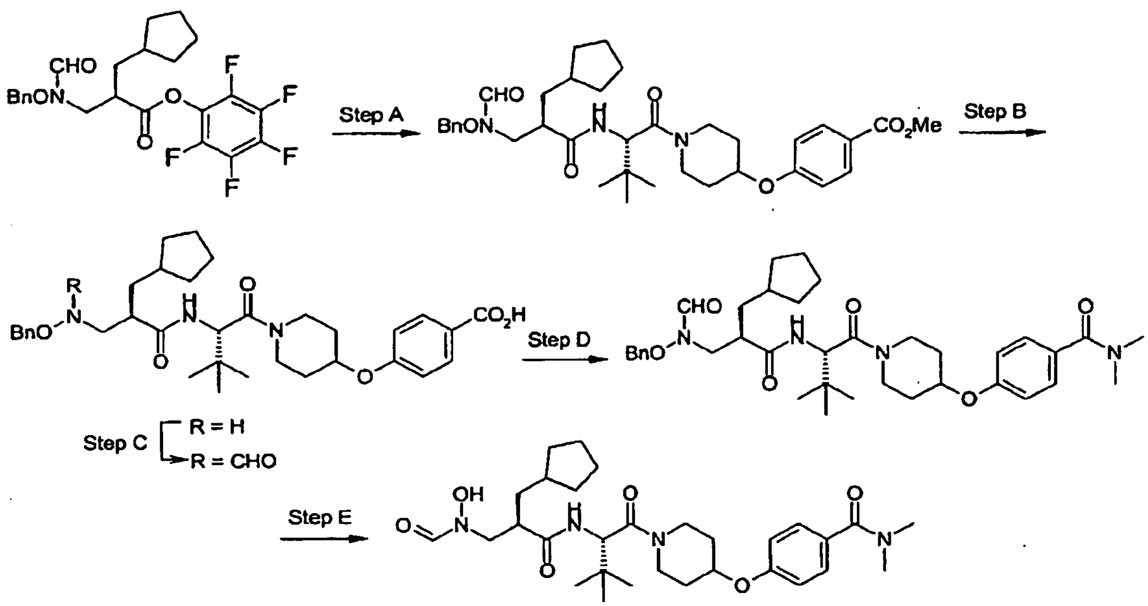
^1H NMR; δ ($CDCl_3$), 7.99 (2H, dd, J_1=1.23 J_2=8.82), 7.35 (5H, m), 6.92 (2H, dd, J_1=1.18 J_2=8.76), 5.58 (1H, m), 5.09 (2H, m), 4.62 (2H, m), 3.89 (4H, m), 3.72 (1H, m), 3.61 (2H, m), 1.90 (4H, m), 0.99 (9H, s); ESMS; +ve ion 505 [M+Na]; HPLC: RT = 6.73 min.

Step C: 4-[1*S*-(2-Amino-3,3-dimethyl-butyryl)-piperidin-4-yloxy]-benzoic acid methyl ester

To a solution of the latter compound (650 mg, 1.35 mmol) in EtOH (10 ml) was added Pd/C (65 mg) and H_2 was bubbled through the resulting suspension for 4 hours. Pd/C was then removed by filtration through a celite pad. The solvent was removed under reduced pressure to give the desired compound in quantitative yield.

^1H NMR; δ ($CDCl_3$), 7.99 (2H, d, J= 8.82), 6.92 (2H, d, J= 8.47), 4.65 (1H, m), 3.89 (3H, s), 3.72 (2H, m), 3.56 (1H, d, J= 4.82), 1.95 (4H, m), 0.99 (9H, s); ESMS; +ve ion 349 [M+1].

Scheme 8



Reagents and conditions: Step A: RHS, NEt_3, DMF; Step B: LiOH, THF, MeOH, H_2O; Step C: FAA, NEt_3, THF; Step D: dimethyl amine, WSC, HOAt, CH_2Cl_2; Step E: Cyclohexene, Pd/C, EtOH, reflux

Step A: 4-(1-{2*S*-[3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-benzoic acid methyl ester

To a solution of the amine (3.4 g, 9.70 mmol) in DMF were added the PFP ester (4 g, 8.50 mmol) followed by NEt_3 (1.3 ml, 9.34 mmol). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude dissolved in ethyl acetate. The work-up was made by means of water, sodium carbonate, ammonium chloride and brine. The combined organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to yield a foam. The crude product was purified through flash chromatography to yield the desired compound as a white foam in 98% yield.

^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.01-7.96 (2H, m), 7.38 (5H, bs), 6.93-6.88 (2H, m), 6.32-6.29 (1H, m), 5.01-4.52 (7H, m), 4.02-3.52 (7H, m), 3.89 (3H, s), 2.68-2.50 (1H, m), 1.98-1.34 (15H, m), 0.95 (9H, s); LRMS: +ve ion 436 [M+H], 658 [M+Na]. HPLC: RT=6.79 min, 98% pure.

Step B: 4-{1-[2*S*-(3-Benzyloxyamino-2*R*-cyclopentylmethyl-propionylamino)-3,3-dimethyl-butyryl]-piperidin-4-yloxy}-benzoic acid

To a cold solution (0°C) of the latter compound (100 mg, 0.16 mmol) in a mixture of THF/MeOH/H_2O (3:1:1; 2.5 ml) was added LiOH (33 mg). The reaction mixture was stirred for 48 hours at room temperature. The solvent was removed under *vacuo* and the crude dissolved in water. The aqueous layer was extracted by means of Et_2O and then acidified to pH=1 by means of HCl 1N. The desired product was then extracted from Et_2O. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to yield the desired compound as a white solid in 61% yield.

^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.06-8.01 (2H, m), 7.38-7.30 (5H, m), 7.09-6.99 (1H, 2d, J=9.3Hz), 6.94-6.89 (2H, m), 5.02 (1H, d, J=9.4Hz), 4.75 (2H, s), 4.69-4.61 (1H, m), 4.08-3.67 (4H, m), 3.58-3.42 (2H, m), 3.17-3.01 (2H, m), 2.62 (1H, m), 2.10-1.40 (15H, m), 1.01 (9H, s); LRMS: +ve ion 594 [M+H], -ve ion 592 [M-1]. HPLC: RT=5.92 min, 98% pure.

Step C: 4-(1-{2*S*-[3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-benzoic acid

To a cold (0°C) of the acid (4.8 g, 8.1 mmol) in THF (100 ml) were added the mixed anhydride (1.8 g, 20.3 mmol) and NEt_3 (3.33 ml, 24.3 mmol). The reaction mixture was stirred at room temperature for 12 hours. The solvent was then removed under reduced pressure and the residue was dissolved in CH_2Cl_2. The organic layer was washed with wate and brine and dried over $MgSO_4$. The solvent was removed in *vacuo* to yield the desired derivative.

^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.19-7.89 (3H, bs), 7.46-7.30 (5H, m), 7.02-6.85 (1H, m), 5.02-4.53 (4H, m), 4.04-3.37 (6H, m), 2.70 (1H, m), 1.98-1.35 (15H, m), 0.97 (9H, s); LRMS: +ve ion 644 [M+Na], -ve ion 620 [M-1] HPLC: RT=6.29 min, 95% pure.

Step D: 4-(1-{2*S*-[3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-N,N-dimethyl-

benzamide

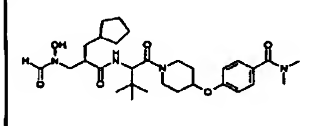
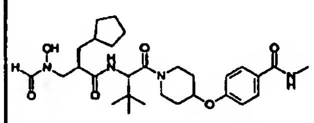
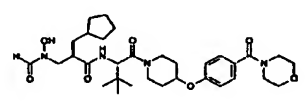
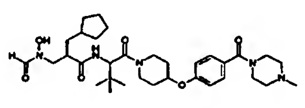
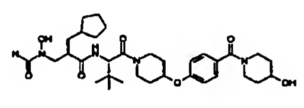
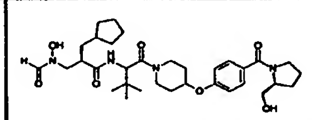
To a cold (0°C)solution of the starting acid (.35 g, 0.56 mmol) in CH_2Cl_2 (8 ml) were added dimethyl amine (0.67 mmol), WSC (118 mg, 0.61 mmol) and HOAt (8 mg, 0.06 mmol). The reaction mixture was stirred at room temperature for 12 hours. Water was added (3 ml) and the resulting solution filtered through polypropylene hydrophobic cartridges (1PS filter). The solvent was then removed under reduced pressure to afford the expected adduct. The crude compound was then purified through flash chromatography to afford a 100% pure compound with a 55% yield.

LRMS: +ve ion 671 [M+Na], HPLC: RT=6.32 min, 100% pure.

Step E: 4-(1*S*-{2-[2*R*-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-*N,N*-dimethyl-benzamide

To a solution of the latter compound (200 mg, 0.31 mmol) were added cyclohexene (0.5 ml) and Pd/C (24 mg). The reaction mixture was stirred to reflux for 3 h. Pd/C was then filtered off through a celite pad. The solvent was removed under reduced pressure to afford the desired adduct as a pure compound. LRMS: +ve ion 581 [M+Na], HPLC: RT=5.49 min, 100% pure.

The compounds of Examples **88a-93** were prepared by the synthetic route outlined in Scheme 9 and as described in detail for Example 88. Step C and Step D were carried out in parallel format for all examples. Characterisation data for the compounds are provided in Table 7.

Table 7			
Example	Structure	Mass Spectral Data	HPLC RT(min)
88		581 (M+Na), 559 (M+1), 557 (M-1).	5.5
88a		545(M+1), 567(M+Na), 543 (M-1).	5.3
89		601 (M+1), 623 (M+Na), 599 (M-1).	5.4
90		614 (M+1), 636 (M+Na), 612 (M-1).	4.8
91		615 (M+1), 637 (M+Na), 613 (M-1).	5.2
92		615 (M+1), 637 (M+Na), 613 (M-1).	5.4

The compounds of Examples 88a - 93 are named as follows:

Example 88a. 4-(1-{2*S*-[3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-N-methyl benzamide

Example 89. 2*R*-Cyclopentylmethyl-*N*-(2,2-dimethyl-1*S*-{4-[4-(morpholine-4-carbonyl)-phenoxy]-piperidine-1-carbonyl}-propyl)-3-(formyl-hydroxy-amino)-propionamide.

Example 90. 2*R*-Cyclopentylmethyl-*N*-(2,2-dimethyl-1*S*-{4-[4-(4-methyl-piperazine-1-carbonyl)-phenoxy]-piperidine-1-carbonyl}-propyl)-3-(formyl-hydroxy-amino)-propionamide.

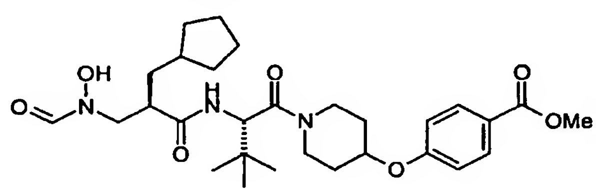
Example 91. 2*R*-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-*N*-(1*S*-{4-[4-(4-hydroxy-piperidine-1-carbonyl)-phenoxy]-piperidine-1-carbonyl}-2,2-dimethyl-propyl)-propionamide.

Example 92. 2*R*-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-*N*-(1*S*-{4-[4-(2*S*-hydroxymethyl-pyrrolidine-1-carbonyl)-phenoxy]-piperidine-1-carbonyl}-2,2-dimethyl-propyl)-propionamide.

Example 93. 4-(1-{2*S*-[2*R*-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-benzoic acid

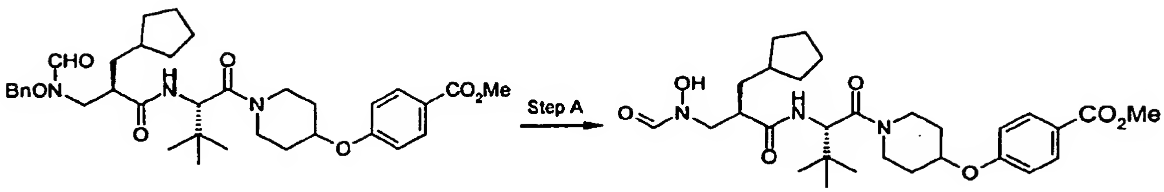
Example 94

4-(1-{2*S*-[2*R*-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-benzoic acid methyl ester



The title compound was prepared as detailed below (see scheme 9) from 4-(1-{2*S*-[3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-benzoic acid methyl ester (scheme 8).

Scheme 9



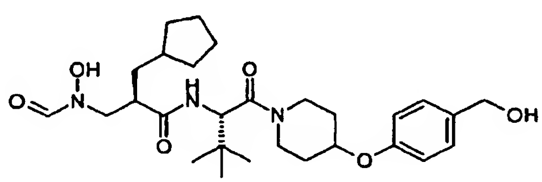
Reagents and conditions: Step A: H_2, Pd/C, EtOH, reflux

To a solution of 4-(1-{2*S*-[3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yloxy)-benzoic acid methyl ester (80 mg, 0.125 mmol) in EtOH (4 ml) was added Pd/C (10 mg). To the resulting suspension, H_2 was bubbled for 2h. Pd/C was filtered off through a celite pad to give the desired compound in 88% yield.

^{1}H NMR δ ($CDCl_3$), 8.40 (0.3H, s), 7.99 (2H, dd, J_1=3.04 J_2=8.85), 7.81 (0.7H, s), 6.91 (2H, dd, J_1=4.87 J_2=8.84), 6.78 (1H, m), 4.94 (1H, m), 4.64 (1H, m), 3.99 (2H, m), 3.89 (3H, s), 3.75 (2H, m), 3.48 (3H, m), 2.81 (1H, m), 2.10-1.32 (13H, m), 1.08 (2H, bs), 0.97 (9H, m); ^{13}C NMR δ ($CDCl_3$), 175.7, 173.6, 170.3, 167.1, 161.2, 132.1, 123.4, 115.5, 72.3, 58.7, 55.1, 54.8, 52.9, 52.3, 44.2, 43.6, 39.2, 39.1, 38.4, 36.6, 35.8, 33.2, 31.6, 31.2, 27.0, 25.5,

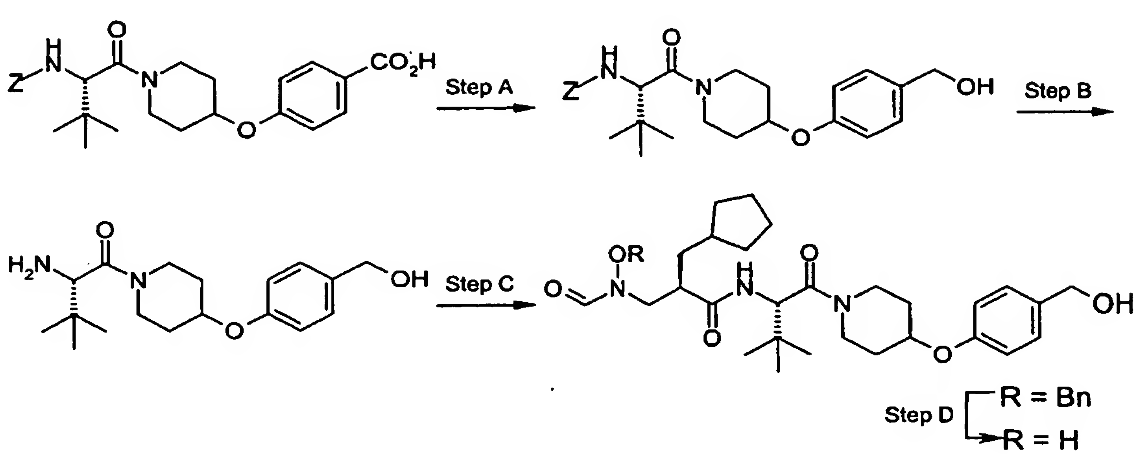
Example 95

2*R*-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-N-{1*S*-[4-(4-hydroxymethyl-phenoxy)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-propionamide



The title compound was prepared as detailed below (see scheme 10) from 4-[1-(2*S*-Benzyloxycarbonylamino-3,3-dimethyl-butyryl)-piperidin-4-yloxy]-benzoic acid

Scheme 10



Reagents and conditions: Step A: BH_3, THF; Step B: H_2, Pd/C, EtOH; Step C: PFP ester, NEt_3 D Step D: H2, Pd/C, EtOH

Step A: {1*S*-[4-(4-Hydroxymethyl-phenoxy)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid benzyl ester

To a cold (10°C) solution of the 4-[1-(2*S*-Benzyloxycarbonylamino-3,3-dimethyl-butyryl)-piperidin-4-yloxy]-benzoic acid (750 mg, 1.6 mmol) in THF (10 ml) was added dropwise BH_3 The reaction mixture was stirred at room temperature for 12 hours. Water was then added dropwise and the solvent removed under reduced pressure. The crude material was taken-up in EtOAc. After filtration, the organic layer was concentrated to yield a white foam as a pure compound in 93% yield.

^{1}H NMR δ ($CDCl_3$), 7.35-7.28 (7H, m), 6.89 (2H, m), 5.60 (1H, m), 5.15-5.03 (2H, AB system), 4.65-4.48 (3H, m), 3.91-3.51 (5H, m), 1.95-1.25 (4H, m), 1.00 (9H, s). ESMS: +ve ion 477 [M+Na], HPLC: RT=6.3 min, 93% pure.

Step B: 2*S*-Amino-1-[4-(4-hydroxymethyl-phenoxy)-piperidin-1-yl]-3,3-dimethyl-butan-1-one

To a solution of the latter compound (680 mg, 1.49 mmol) in EtOH (10 ml) was added Pd/C (68 mg) and H_2 was bubbled through the resulting suspension for 2 hours. The reaction mixture was then stirred for two hours under a blanket of H_2. Pd/C was then

filtered off through a celite pad. The solvent was removed under reduced pressure to give the desired compound in 94% yield. ^{1}H NMR δ ($CDCl_3$), 7.29-6.86 (4H, AB system), 4.62 (2H, s), 4.55 (1H, m), 3.82-3.58 (2H, m), 1.92-1.73 (11H), 1.00 (9H, s). ESMS: +ve ion 321 [M+1].

Step C: 3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-N-{1*S*-[4-(4-hydroxymethyl-phenoxy)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-propionamide

To a solution of the latter compound, were added PFP ester (635 mg, 1.35 mmol) and NEt_3 (193 ml, 1.41 mmol). The reaction mixture was then stirred for 12 hours. DMF was removed under reduced pressure and the crude material was taken-up in EtOAc, washed with water, sodium carbonate (1N), saturate aqueous solution of NH_4Cl and brine. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification through flash chromatography the desired adduct was obtained as a white foam in 63% yield. ^{1}H NMR; δ ($CDCl_3$), 8.13 (0.25H, m), 7.88 (0.25H, m), 7.38 (5H, s), 7.27 (2.5H, m), 6.87 (2H, m), 6.32 (1H, m), 4.89 (3H, m), 4.56 (3H, m), 3.96 (1H, m), 3.73 (2H, m), 3.45 (1H, m), 2.60 (1H, m), 2.06-1.31 (15H, m), 1.06 (11H, m); ESMS: +ve ion 630 [M+Na], HPLC: RT=6.31 min, 100% pure.

Step D: 2*R*-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-N-{1*S*-[4-(4-hydroxymethyl-phenoxy)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-propionamide

To a solution of the latter compound (50 mg, 0.08 mmol) in MeOH (3 ml) were added HCO_2NH_4 (26 mg, 0.41 mmol) and Pd/C (5 mg). The resulting suspension was stirred for 2 hours. Pd/C was filtered off. The solvent was removed under reduced pressure and the crude material taken-up in EtOAc, washed with water and brine. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield the expected compound in 62% yield. ^{1}H NMR; δ ($CDCl_3$), 8.39 (0.3H, s), 7.81 (0.7H, s), 7.29 (2H, dd, J_1=3.47 J_2=9.11), 6.89 (2H, dd, J_1=3.64 J_2=8.55), 6.73 (1H, m), 4.94 (1H, m), 4.62 (3H, m), 4.01 (2H,m), 3.76 (2H, m), 3.48 (3H, m), 2.74 (1H, m), 2.08-1.35 (19H, m), 1.02 (13H, m); ESMS: +ve ion 540 [M+Na], -ve ion 516 [M-1] HPLC: RT=5.49 min, 100% pure.

Biological Example

Minimal inhibitory concentrations (MIC) of compounds of the invention against *E. coli* strain DH5α (Genotype; F-φ80d*lac*ZΔM15Δ(*lac*ZYA-*arg*F)U169 *deo*R *rec*A1 *end*A1 *hsd*R17(r_K^-, m_K^+)*pho*A *sup*E44λ$^-$ *thi*-1 *gyr*A96 *rel*A1) obtained from GibcoBRL Life Technologies, or *Staphylococcus capitis* (American Type Culture Collection number 35661) were determined as follows. Stock solutions of each test compound were prepared by dissolution of the compound in dimethylsulfoxide at 10mM. For the determination of the minimal inhibitory concentration, two fold serial dilutions were prepared in 2xYT broth (typtone 16g/1, yeast extract 10g/1, sodium chloride 5g/1 obtained from BIO 101 Inc, 1070 Joshua Way, Vista, CA92083, USA) to yield 0.05 ml compound-containing medium per well. Inocula were prepared from cultures grown overnight in 2xYT broth at 37°C. Cell densities were adjusted to absorbance at 660nm (A_{660}) = 0.1; the optical density-standardised preparations were diluted 1:1000 in 2xYT broth; and each well inoculated with 0.05ml of the diluted bacteria. Microtiter plates were incubated at 37°C for 18 hours in a humidified incubator. The MIC (μM) was recorded as the lowest drug concentration that inhibited visible growth.

In general, the compounds of the Examples were more active against the Gram positive *S. capitis* than the Gram negative *E. coli*. Results for some of the compounds of the Examples are reported in Table 8:

Table 8

Example No.	E. Coli MIC (μM)	S. Capitis (μM)
24	>200, <400	100
29	100	>200, <400
44	200	12

50	200	6.2
52	200	6.2
54	200	3.1
55	200	6.2
56	50	25
57	100	6.2
69	200	25
74	200	25
78	>200, <400	200
79	>200, <400	6.25
88	100	6.2
89	200	25
91	200	25

Using the above protocol for establishing the MIC values against *S. capitis*, it appears that in general compounds of the invention of formula (II) wherein Q is a hydroxamate group have activities comparable to compounds of similar structure wherein Q is an N-formylhydroxylamine group.

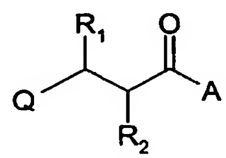
In another experiment, the MICs of the compound of Example 91 were determined against certain respiratory tract pathogens, using the Microdilution Broth Method according to the approved standard of the National Committee for Clinical Laboratory Standards procedure (Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically - Fourth Edition ISBN 1-56238-309-4). The results appear in Table 9.

Table 9

Organism	MIC (μg/ml)
Moraxella catarrhalis 2413	0.25
Moraxella catarrhalis 2412	0.5
Haemophilus Infuenzae 1414	4
Haemophilus Infuenzae 1390	1
Streptococcus pneumoniae (PRP) 2390	0.25
Streptococcus pneumoniae (PIP) 2391	0.25
Streptococcus pneumoniae (PSP) 2403	0.25

Claims:

1. A compound of formula (II), or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof



(II)

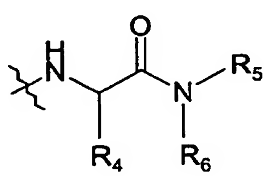
wherein

Q represents a radical of formula -N(OH)CH(=O) or formula -C(=O)NH(OH);

R_1 represents hydrogen, C_1-C_6 alkyl or C_1-C_6 alkyl substituted by one or more halogen atoms, or, except when Q is a radical of formula -N(OH)CH(=O), a hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkenyloxy, amino, C_1-C_6 alkylamino, or di-(C_1-C_6 alkyl)amino group;

R_2 represents a substituted or unsubstituted C_1-C_6 alkyl, cycloalkyl(C_1-C_6 alkyl)- or aryl(C_1-C_6 alkyl)- group;

and A represents a group of formula (IIA), or (IIB):



(IIA) (IIB)

wherein R_4 represents the side chain of a natural or non-natural alpha amino acid, and R_5 and R_6 when taken together with the nitrogen atom to which they are attached form a saturated heterocyclic first ring of 5 to 7 atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7

atoms; characterised in that

(a) the said second ring is substituted by $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkoxy, hydroxy, mercapto, $(C_1\text{-}C_6)$alkylthio, halo, amino, trifluoromethyl, oxo, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a $(C_1\text{-}C_6)$alkyl group; and/or

(b) the said first or second ring is substituted by a group of formula (IIC), provided that the first ring is not substituted by phenoxy, benzyl or benzyl substituted by $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, phenoxy, hydroxy, mercapto, $(C_1\text{-}C_6)$alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a $(C_1\text{-}C_6)$alkyl group,

$$-(Alk^1)_m\text{-}(X)_p\text{-}(Alk^2)_n\text{—}Z \qquad \text{(IIC)}$$

wherein
m, p and n are independently 0 or 1;

Z represents, a hydroxy group, or a phenyl or heterocyclic ring of 5 to 7 atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 atoms

Alk^1 and Alk^2 independently represent divalent $C_1\text{-}C_3$ alkylene radicals;

X represents -O-, -S-, -S(O)-, $-S(O_2)-$, -C(=O)-, -NH-, $-NR_7-$ where R_7 is $C_1\text{-}C_3$ alkyl;

and wherein
Alk^1, Alk^2 and Z when Z is not a hydroxy group independently are optionally

substituted by

$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl,

phenyl, or halophenyl,

trifluoromethyl,

monocyclic 5 or 6-membered hetrocyclic,

benzyl, or halophenylmethyl,

hydroxy, phenoxy, $(C_1\text{-}C_6)$alkoxy, or hydroxy$(C_1\text{-}C_6)$alkyl,

mercapto, $(C_1\text{-}C_6)$alkylthio or mercapto$(C_1\text{-}C_6)$alkyl,

oxo,

nitro,

cyano (-CN)

halo (bromo, chloro, fluoro, or iodo)

-COOH, or -COOR^A,

-CONH$_2$, -CONHR^A, or -CONR^{A}R^B

-COR^A, -SO$_2$R^A,

-NHCOR^A,

-NH$_2$, -NHR^A, or -NR^{A}R^B,

wherein R^A and R^B are independently a $(C_1\text{-}C_6)$ alkyl group, R^A and R^B taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring which may be substituted by (C_1C_3)alkyl, hydroxy, or hydroxy$(C_1\text{-}C_3)$alkyl.

2. A compound as claimed in claim 1 wherein

(a) the said second ring is substituted by $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkoxy, hydroxy, mercapto, $(C_1\text{-}C_6)$alkylthio, amino, trifluoromethyl, oxo, nitro, -COOH, -CONH$_2$, -COR^A, -COOR^A, -NHCOR^A, -CONHR^A, -NHR^A, -NR^{A}R^B, or -CONR^{A}R^B wherein R^A and R^B are independently a $(C_1\text{-}C_6)$alkyl group; and/or

(b) the said first or second ring is substituted by a group of formula (IIC), provided that the first ring is not substituted by phenoxy, benzyl or benzyl substituted by (C_1-C_6)alkyl, (C_1-C_6)alkoxy, phenoxy, hydroxy, mercapto, (C_1-C_6)alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group,

$$-\!\!\!\!\wr\!-(Alk^1)_m-(X)_p-(Alk^2)_n-Z \qquad \text{(IIC)}$$

wherein
m, p and n are independently 0 or 1;

Z represents, a hydroxy group, or a phenyl or heterocyclic ring of 5 to 7 atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 atoms

Alk^1 and Alk^2 independently represent divalent C_1-C_3 alkylene radicals;

X represents -O-, -S-, -S(O)-, $-S(O_2)-$, -C(=O)-, -NH-, $-NR_7-$ where R_7 is C_1-C_3 alkyl;

and wherein
Alk^1, Alk^2 and Z when Z is not a hydroxy group independently are optionally substituted by

(C_1-C_6)alkyl, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl,
phenyl, or halophenyl,
trifluoromethyl,
monocyclic 5 or 6-membered hetrocyclic,
benzyl,
hydroxy, phenoxy, or (C_1-C_6)alkoxy,

mercapto, or (C_1-C_6)alkylthio,

oxo,

nitro,

-COOH, or -$COOR^A$,

-$CONH_2$, -$CONHR^A$, or -$CONR^AR^B$

-COR^A,

-$NHCOR^A$,

-NH_2, -NHR^A, or -NR^AR^B,

wherein R^A and R^B are independently a (C_1-C_6) alkyl group,

3. A method for the treatment of bacterial infections in humans and non-human mammals, which comprises administering to a subject suffering such infection an antibacterially effective dose of a compound as claimed in claim 1 or claim 2.

4. A method for the treatment of bacterial contamination by applying an antibacterially effective amount of a compound as claimed in claim 1 or claim 2 to the site of contamination.

5. The use of a compound as claimed in claim 1 or claim 2 in the manufacture of an antibacterial composition.

6. A pharmaceutical or veterinary composition comprising a compound as claimed in claim 1 or claim 2 together with a pharmaceutically of veterinarily acceptable carrier.

7. A compound as claimed in claim 1 or claim 2, a method as claimed in claim 3 or claim 4, the use as claimed in claim 5 or a composition as claimed in claim 6 wherein R_1 is hydrogen.

8. A compound, method, use or composition as claimed in claim 7 wherein R_2 is (C_1-C_6)alkyl-, cycloalkylmethyl-, (C_1-C_3)alkyl-S-(C_1-C_3)alkyl-, or (C_1-C_3)alkyl-O-$(C_1$-

C_3)alkyl-.

9. A compound, method, use or composition as claimed in claim 7 wherein R_2 is n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

10. A compound as claimed in claim 1 or claim 2, a method as claimed in claim 3 or claim 4, the use as claimed in claim 5 or a composition as claimed in claim 6 wherein R_4 is

the characterising group of a natural α amino acid, for example benzyl, or 4-methoxyphenylmethyl, in which any functional group may be protected, any amino group may be acylated and any carboxyl group present may be amidated; or

a group -[Alk]$_n$$R_9$ where Alk is a (C_1-C_6)alkylene or (C_2-C_6)alkenylene group optionally interrupted by one or more -O-, or -S- atoms or -N(R_{12})- groups [where R_{12} is a hydrogen atom or a (C_1-C_6)alkyl group], n is 0 or 1, and R_9 is hydrogen or an optionally substituted phenyl, aryl, heterocyclyl, cycloalkyl or cycloalkenyl group or (only when n is 1) R_9 may additionally be hydroxy, mercapto, (C_1-C_6)alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, -$CONH_2$, -$COOR^A$, -$NHCOR^A$, -$CONHR^A$, -NHR^A, -NR^AR^B, or -$CONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group; or

a benzyl group substituted in the phenyl ring by a group of formula -OCH_2COR_8 where R_8 is hydroxyl, amino, (C_1-C_6)alkoxy, phenyl(C_1-C_6)alkoxy, (C_1-C_6)alkylamino, di((C_1-C_6)alkyl)amino, phenyl(C_1-C_6)alkylamino; or

a heterocyclic(C_1-C_6)alkyl group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, (C_1-C_6)alkoxy, cyano, (C_1-C_6)alkanoyl, trifluoromethyl (C_1-C_6)alkyl, hydroxy, formyl, amino,

(C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, mercapto, (C_1-C_6)alkylthio, hydroxy(C_1-C_6)alkyl, mercapto(C_1-C_6)alkyl or (C_1-C_6)alkylphenylmethyl; or

a group $-CR_aR_bR_c$ in which:

each of R_a, R_b and R_c is independently hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl; or

R_c is hydrogen and R_a and R_b are independently phenyl or heteroaryl such as pyridyl; or

R_c is hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, or (C_3-C_8)cycloalkyl, and R_a and R_b together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

R_a, R_b and R_c together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

R_a and R_b are each independently (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, or a group as defined for R_c below other than hydrogen, or R_a and R_b together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and R_c is hydrogen, -OH, -SH, halogen, -CN, $-CO_2H$, (C_1-C_4)perfluoroalkyl, $-CH_2OH$, $-CO_2(C_1-C_6)$alkyl, $-O(C_1-C_6)$alkyl, $-O(C_2-C_6)$alkenyl, $-S(C_1-C_6)$alkyl, $-SO(C_1-C_6)$alkyl, $-SO_2(C_1-C_6)$ alkyl, $-S(C_2-C_6)$alkenyl, $-SO(C_2-C_6)$alkenyl, $-SO_2(C_2-C_6)$alkenyl or a group -Q-W wherein Q represents a bond or -O-, -S-, -SO- or $-SO_2-$ and W represents a phenyl, phenylalkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkylalkyl, (C_4-C_8)cycloalkenyl, (C_4-C_8)cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, -

CO_2H, $-CO_2(C_1-C_6)$alkyl, $-CONH_2$, $-CONH(C_1-C_6)$alkyl, $-CONH(C_1-C_6$alkyl$)_2$, -CHO, $-CH_2OH$, (C_1-C_4)perfluoroalkyl, $-O(C_1-C_6)$alkyl, $-S(C_1-C_6)$alkyl, $-SO(C_1-C_6)$alkyl, $-SO_2(C_1-C_6)$alkyl, $-NO_2$, $-NH_2$, $-NH(C_1-C_6)$alkyl, $-N((C_1-C_6)$alkyl$)_2$, $-NHCO(C_1-C_6)$alkyl, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, phenyl or benzyl.

11. A compound, method, use or composition as claimed in claim 9 or claim 10 wherein R_4 is methyl, ethyl, n-propyl, n-butyl, benzyl, 4-chlorobenzyl, 4-hydroxybenzyl, phenyl, cyclohexyl, cyclohexylmethyl, pyridin-3-ylmethyl, tert-butoxymethyl, naphthylmethyl, iso-butyl, sec-butyl, tert-butyl, 1-benzylthio-1-methylethyl, 1-methylthio-1-methylethyl, 1-mercapto-1-methylethyl, 1-methoxy-1-methylethyl, 1-hydroxy-1-methylethyl, 1-fluoro-1-methylethyl, hydroxymethyl, 2-hydroxethyl, 2-carboxyethyl, 2-methylcarbamoylethyl, 2-carbamoylethyl, or 4-aminobutyl.

12. A compound, method, use or composition as claimed in claim 9 or claim 10 wherein R_4 is tert-butyl, iso-butyl, benzyl, isopropyl or methyl.

13. A compound, method, use or composition as claimed in claim 12 wherein R_5 and R_6 taken together with the nitrogen atom to which they are attached form a piperidin-1-yl or 1-piperazin-4-yl ring.

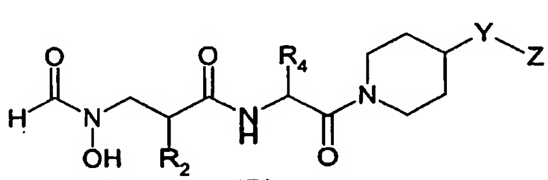
14. A compound, method, use or composition as claimed in any of claims 9, 12 or 13 wherein the substituent (IIC) has the formula $-CH_2Z$, -OZ, or -(C=O)Z wherein Z is as defined in claim 1 or claim 2

15. A compound, method, use or composition as claimed in any of claims 9 or 12-14 wherein in the substituent (IIC) Z is a phenyl, 3,4-methylenedioxyphenyl, morpholinyl, pyrimidinyl, 1,2,3-thiadiazolyl, 1,4-thiazolyl, benzofuranyl, furanyl, thienyl, pyranyl, pyrrolyl, pyrazolyl, isoxazolyl, or pyridyl ring which may optionally be substituted as specified in the definition of Z in claim 1 or claim 2

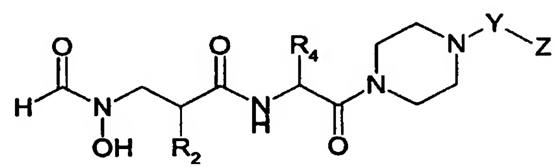
16. A compound, method, use or composition as claimed in any of claims 9 or 12-14 wherein in the substituent (IIC) Z is a phenyl, 3,4-methylenedioxyphenyl, morpholinyl, pyrimidin-2-yl, 1,2,3-thiadiazol-5-yl, 1,4-thiazol-5-yl, benzofuran-2-yl, 2- or 3-furanyl, 2- or 3-thienyl, 2- or 3-pyranyl, 2-, 3- or 4-pyrrolyl, 3-, 4- or 5-pyazolyl, 3-, 4- or 5-isoxazolyl, or 2-, 3- or 4-pyridyl ring which may optionally be substituted as specified in the definition of Z in claim 1 or claim 2.

17. A compound as claimed in claim 1, a method as claimed in claim 2 or claim 3, the use as claimed in claim 4 or a composition as claimed in claim 5 wherein R_1 is hydrogen; R_2 is n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl; R_4 is tert-butyl, iso-butyl, benzyl or methyl; R_5 and R_6 taken together with the nitrogen atom to which they are attached form a piperidin-1-yl or 1-piperazin-4-yl ring; the substituent (IIC) has the formula $-CH_2Z$, -OZ, or -(C=O)Z wherein Z is as defined in claim 16 or claim 17.

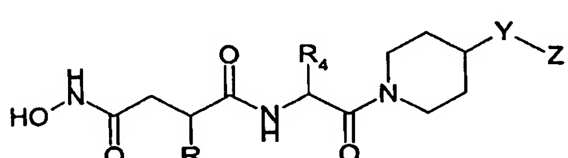
18. A compound as claimed in claim 1 or claim 2, a method as claimed in claim 3 or claim 4, the use as claimed in claim 5 or a composition as claimed in claim 6 wherein the compound is one selected from the group consisting of compounds of formulae (IID) - (IIG) and (IIW) - (IIZ):



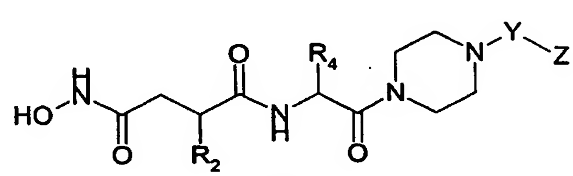
(IID)



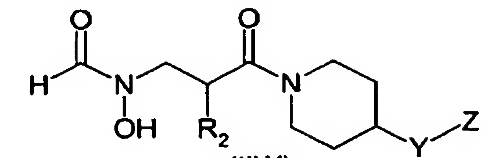
(IIE)



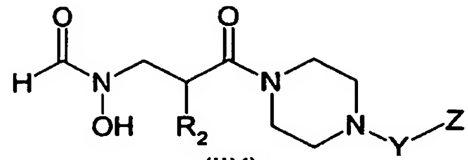
(IIF)



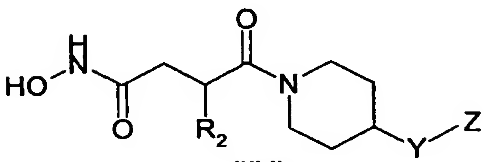
(IIG)



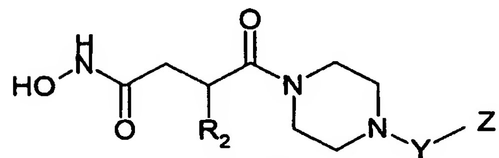
(IIW)



(IIX)



(IIY)



(IIZ)

wherein

R_2 is n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl;

R_4 is tert-butyl, iso-butyl, benzyl or methyl;

Y is $-CH_2-$, -O- or -(C=O)-; and

Z is as defined in claim 16 or 17.

19. A compound as claimed in claim 1 or claim 2, a method as claimed in claim 3 or claim 4, the use as claimed in claim 5 or a composition as claimed in claim 6 wherein the compound is one specifically named and/or exemplified herein, or is the hydroxamate (Q represents a radical of formula -C(=O)NH(OH)) or N-formylhydroxylamine (Q represents a radical of formula -N(OH)CH(=O)) analogue thereof, as the case may be.

20. A compound as claimed in claim 1 or claim 2, a method as claimed in claim 3 or claim 4, the use as claimed in claim 5 or a composition as claimed in claim 6 wherein the compound is *N*-[1*S*-(4-benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-2*R*-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide or *N*-[1*S*-(4-benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-2*R*-cyclopentylmethyl-*N*-hydroxy-succinamide.

AMENDED CLAIMS
[received by the International Bureau on 20 February 2001 (20.02.01);
original claims 1 and 2 amended; remaining claims unchanged (2 pages)]

atoms; characterised in that

(a) the said second ring is substituted by (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkoxy, hydroxy, mercapto, (C_1-C_6)alkylthio, halo, amino, trifluoromethyl, oxo, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group; and/or

(b) the said first or second ring is substituted by a group of formula (IIC), provided that the first ring is not substituted by phenoxy, benzyl or benzyl substituted by (C_1-C_6)alkyl, (C_1-C_6)alkoxy, phenoxy, hydroxy, mercapto, (C_1-C_6)alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group,

$$-(Alk^1)_m-(X)_p-(Alk^2)_n-Z \qquad (IIC)$$

wherein
m, p and n are independently 0 or 1;

Z represents a phenyl or heterocyclic ring of 5 to 7 atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 atoms

Alk^1 and Alk^2 independently represent divalent C_1-C_3 alkylene radicals;

X represents -O-, -S-, -S(O)-, $-S(O_2)-$, -C(=O)-, -NH-, $-NR_7-$ where R_7 is C_1-C_3 alkyl;

and wherein
Alk^1, Alk^2 and Z independently are optionally substituted by

(b) the said first or second ring is substituted by a group of formula (IIC), provided that the first ring is not substituted by phenoxy, benzyl or benzyl substituted by (C_1-C_6)alkyl, (C_1-C_6)alkoxy, phenoxy, hydroxy, mercapto, (C_1-C_6)alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group,

$$-(Alk^1)_m-(X)_p-(Alk^2)_n-Z \qquad (IIC)$$

wherein
m, p and n are independently 0 or 1;

Z represents a phenyl or heterocyclic ring of 5 to 7 atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 atoms

Alk^1 and Alk^2 independently represent divalent C_1-C_3 alkylene radicals;

X represents -O-, -S-, -S(O)-, $-S(O_2)-$, -C(=O)-, -NH-, $-NR_7-$ where R_7 is C_1-C_3 alkyl;

and wherein
Alk^1, Alk^2 and Z independently are optionally substituted by

(C_1-C_6)alkyl, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl,
phenyl, or halophenyl,
trifluoromethyl,
monocyclic 5 or 6-membered hetrocyclic,
benzyl,

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/03078

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	C07D211/32	C07D401/04	C07D317/58	C07D211/16	C07D295/18
	C07D307/68	C07D405/14	C07D217/06	C07D239/42	C07D211/22
	C07D213/74	C07D209/08	C07D317/68	C07D213/38	C07D211/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BROUGHTON ET AL.: "Studies concerning the Antibiotic Actinonin" J. CHEM. SOC. PERKIN TRANS I, vol. 9, 1975, pages 857-60, XP002157880 Table 3 ---	1-17
X	DEVLIN, JOHN P. ET AL: "Antibiotic actinonin. V. Synthesis of structural analogs of actinonin b the anhydride-ester method" J. CHEM. SOC., PERKIN TRANS. 1 (1975), (9), 846-8 , XP002157881 table 2 ---	1-12,14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 January 2001	06/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Diederen, J

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/03078

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/506 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PENNING, THOMAS D. ET AL: "Kelatorphan and related analogs: potent and selective inhibitors of leukotriene A4 hydrolase" BIOORG. MED. CHEM. LETT. (1995), 5(21), 2517-22 , XP002157882 page 2517 table 1 ---	1-20
P,X	WO 99 39704 A (BRITISH BIOTECH PHARM ;DAVIES STEPHEN JOHN (GB); HUNTER MICHAEL GE) 12 August 1999 (1999-08-12) cited in the application examples 30,46 abstract ---	1-12,14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 January 2001	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Diederen, J

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 57097 A (NGU KHEHYONG ;PATEL DINESH V (US); VERSICOR INC (US)) 11 November 1999 (1999-11-11) abstract page 4, line 18 -page 5, line 6 figure 22	1-12,14
X	WO 91 02716 A (BRITISH BIO TECHNOLOGY) 7 March 1991 (1991-03-07) abstract examples 2,4,5,16	1,2, 6-12,14
X	JP 08 053403 A (FUJISAWA PHARMACEUT CO LTD) 27 February 1996 (1996-02-27) abstract Compd 1d R3=CH3, R5=4-hydroxy-1-piperidinyl, R4=2-pyridinyl page 24	1-14
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X	INAOKA, ET AL.: "Propioxatins A and B, new enkephalinase B inhibitors." J. BIOCHEM. (TOKYO), vol. 104, 1988, pages 706-11, XP000978993 table I, compd 4	1,2,6,7
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2

INTERNATIONAL SEARCH REPORT

ormation on patent family members

Interr ·nal Application No
PCT/GB 00/03078

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			BR	9907689	A	14-11-2000
			EP	1052984	A	22-11-2000
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			ES	2063975	T	16-01-1995
			JP	2871849	B	17-03-1999
			JP	5501864	T	08-04-1993
			NO	920702	A	23-04-1992
			NZ	235050	A	23-12-1991
			US	5910609	A	08-06-1999
			US	5453438	A	26-09-1995
JP 08053403	A	27-02-1996	NONE			